
**“EFFECTIVENESS OF MIFEPRISTONE AND
MISOPROSTOL V/S MISOPROSTOL ALONE
IN THE INDUCTION OF LABOR –
A RANDOMIZED CONTROLLED TRIAL”**

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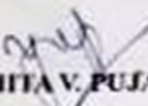
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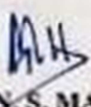
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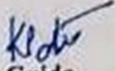
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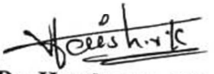

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LIST OF ABBREVIATIONS USED

IOL	- Induction of labor
TAB	- Tablet
LMIC	- low- and middle-income countries
PG	- prostaglandin
ACOG	- American College of Obstetricians and Gynecologists
LSCS	-Lower segment caesarean section
CI	- Confidence interval
EFM	- Electronic fetal monitoring
HR	- Hazard ratio
HELLP	- Hemolysis/elevated liver enzymes/low platelets
FGR	- Fetal growth restriction
HTN	- Hypertension
IUGR	- Intrauterine growth restriction
NICHD	- National Institute of Child Health and Human Development
NICU	- Neonatal intensive care unit
OR	- Odds ratio
CPD	- Cephalo pelvic disproportion
CDMR	- Caesarean delivery on maternal request
MSL	- Meconium Stained Liquor
PROM	- Premature rupture of membranes

PGE1	- Prostaglandin E1 (misoprostol)
PGE2	- Prostaglandin E2 (dinoprostone)
RCT	- Randomized clinical trial
RR	- Relative risk
SMFM	- Society for Maternal-Fetal Medicine
NSAIDS	- nonsteroidal anti-inflammatory drugs
AMTSL	- Active management of third stage of labour

ABSTRACT

“Effectiveness of Mifepristone and Misoprostol V/S Misoprostol alone in induction of labor: A randomized controlled trial”

Objective: To determine the effectiveness of Mifepristone and Misoprostol V/S Misoprostol alone in “induction of labor” and feto-maternal outcome.

Methods: The present hospital based randomized controlled “study” conducted on 226 women (113 in Group A and B each). Group A- Tab. Mifepristone +Tab. Misoprostol, Group B- Tab. Misoprostol.

Results: Pre induction Bishops score was significantly higher in Group B compared to Group A ($p < 0.05$). In 19.5% women from Group A had fetal distress as indication of LSCS as compared to 11.5% from Group B. 13.3% women from Group A had failed induction as indication of LSCS as compared to 26.5% from Group B. 59.3% of the pregnant women from Group A went into active labour as compared to 55.8% from Group B ($p > 0.05$). 55.8% of the pregnant women from Group A delivered with normal vaginal delivery as compared to 47.8% from Group B. 44.2% of the pregnant women from Group A underwent LSCS as mode of delivery as compared to 52.2% from Group B ($p > 0.05$).

Conclusion: In this study we found clinically significant improvement (though not statistically significant) in Bishops score in group A (Tab. Mifepristone with Tab. Misoprostol) compare with Group B (Tab. Misoprostol) in induction of labour.

Key words: Tab. mifepristone and misoprostol VS Tab. misoprostol, induction of labor

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INTRODUCTION

Induction of labour (IOL) is the process of initiating contractions in pregnant persons who are currently not in labour, to help them achieve vaginal delivery within 24 to 48 hours. Cervical ripening is one of the methods used for labour induction; it is “the use of pharmacological or other means to soften, efface, or dilate the cervix to increase the likelihood of a vaginal delivery.”¹

Induction of labor (IOL) is a common obstetric intervention that stimulates the onset of labor using artificial methods.¹ Rates of labor induction have nearly doubled since 1990.² There is substantial variation in IOL rates worldwide, and this can be attributed to variability in the guidelines and lack of consensus on the clinical practice guidelines on IOL. Nowadays, in high- income countries, the proportion of neonates born following IOL is estimated to be approximately 25%. In contrast, the corresponding rates are generally lower in low-and middle-income countries (LMIC).¹

One of the most common indications for labour induction is prolonged pregnancy as it is associated with the increased risk to the fetus, including increased perinatal mortality rate, low 5-min Apgar scores, dysmaturity syndrome, and increased risk of death within the first year of life. Successful induction, despite availability of multiple induction agents and advances in medical technology and knowledge can still present as a challenge in the modern era. While modern medical advancements have certainly improved our ability to induce labor safely and effectively, the process still remains a complex and nuanced aspect of obstetric care that requires careful consideration of various clinical, ethical, and patient-related factors.

Mifepristone is a steroidal compound that has anti glucocorticoid and antiprogestosterone properties. It increases uterine activity and causes cervical effacement and dilatation for pregnancy termination. The pharmacokinetics of mifepristone is characterized by rapid absorption and a long half-life of 25–30 h.³ Mifepristone now has an established role in termination of pregnancy during the early first, and the second trimesters.⁴

Animal studies have suggested that mifepristone may also have a role in inducing labor in late pregnancy. Hapangama and Neilson⁵ in Cochrane collaboration published in 2009 are of the opinion that there is insufficient information available from clinical trials to support the use of mifepristone to induce labor. Keeping this in mind, the present study was undertaken to find out the safety and efficacy of mifepristone for pre-induction cervical ripening and labor induction in women with prolonged pregnancy.

Tablet Mifepristone is also called as RU (Roussel Uclaf) - 486. It is 19 – nor steroid with potent competitive anti-progesterone and significant anti-glucocorticoid activity. Mifepristone is used as a pretreatment to prime the cervix adequately.⁶

Mifepristone produced a modification in the consistency of the cervix with a statistical improvement in cervical calibration.⁷ Mifepristone causes blockage of progesterone receptors and inhibits the activity of progesterone at cellular level with potent anti progestogenic, anti- glucocorticoid and a weak anti androgenic action and causes cervical ripening effect.⁸ Mifepristone has minimal effects on uterine contractility and increase the sensitivity to prostaglandins and convert the quiet pregnant uterus into organ of spontaneous activity.⁹

The role of mifepristone in inducing labor when the fetus is viable is being evaluated.¹⁰⁻¹⁴ Mifepristone in doses of 200 to 400 mg has been shown to improve cervical ripening and rates of spontaneous labor, with no apparent maternal or neonatal adverse effects. In these studies, if ripening with a prostaglandin was required after cervix priming with mifepristone, either misoprostol, a prostaglandin (PG) E1 analogue, or PGE2 was administered vaginally. The anti- glucocorticoid properties of mifepristone have not been found to be of clinical significance in adult women, even at the dose of 2 g per day¹⁵, and no cases of significant neonatal hypoglycemia have been reported so far.

Various studies conducted on induction of labor in live term pregnancies with Mifepristone in doses of 200-400 mg has shown to improve cervical ripening and rates of induction of labor with no apparent maternal or fetal side effects.¹⁶⁻¹⁹ Also some studies have shown that combined Mifepristone with Misoprostol is safe, efficient and economical and convenient induction agent for initiation of labor,²⁰ but the cesarean section rate was significantly lower in induction with Mifepristone alone but found more with Mifepristone followed by tablet Misoprostol.²⁰

Misoprostol is a synthetic analogue of prostaglandin E1, which has gastric antisecretory and mucosal protective effects. Misoprostol also has uterotonic properties, by contracting smooth muscle fibers in the myometrium and relaxation of the cervix, facilitating cervical opening.²¹

Misoprostol tablets, administered orally and vaginally, are used for the induction of labour or cervical ripening, but are not currently approved by Health Canada for this indication. The usual dose is 50 mcg orally or 25 mcg vaginally, which may be repeated every 4 hours if contractions are absent or not painful.²¹

Prostaglandins are widely used to prepare the unfavourable cervix for parturition. However, prostaglandins preparations may have their own side effects and sometimes might fail to produce sufficient cervical ripening for induction to proceed.

Hence the present study was planned with the objective to find out the effectiveness of Mifepristone-Misoprostol over misoprostol alone in inducing labor and if mifepristone proves to be an effective and safe inducing agent then it can be used as a safe and effective method for IOL.

AIMS AND OBJECTIVES

Primary Objective: To determine the effect of Mifepristone and Misoprostol V/S Misoprostol alone in induction of labor.

Secondary Objective: To determine the maternal- perinatal outcomes.

Hypothesis

Primary hypothesis: There may be some difference in the effect of combination therapy of Tab. Mifepristone and Misoprostol V/S Misoprostol alone with respect to induction of labor.

Secondary hypothesis: There may be some difference in the effect of combination therapy of Tab. Mifepristone and Misoprostol V/S Misoprostol alone with respect to fetomaternal outcomes.

REVIEW OF LITERATURE

Induction of labor refers to techniques for stimulating uterine contractions to accomplish delivery prior to the spontaneous onset of such contractions. Clinicians recommend induction to patients when they believe allowing the pregnancy to continue is at least as risky for the mother and/or fetus/newborn as delivery.²²

Induction of labour (IOL) is the artificial initiation of uterine contraction by various means such as medical, surgical or mechanical to achieve vaginal delivery. Misoprostol, a prostaglandin E1 analogue is used popularly for IOL in resource-limited health centres. It is a common obstetrics intervention performed when the continuation of pregnancy is not desired.²²

The IOL rate varies from different parts of the world. In the United States, the rate has risen steadily from 9.6-27.1 of all birth from 1990-2018.²³ The rate of induction in Nepal was reported between 8.9% to 10.5% by different authors.^{24,25} Induction is indicated when benefits outweigh the harms more to mother and fetus than induction itself.²⁶ IOL may sometimes have adverse effects on the health of the mother and fetus if a selection of cases and their monitoring is not done properly.

Statement of the problem

As compared with expectant management, induction of labor (IOL) might be associated with better maternal and perinatal outcomes as well as adverse outcome depending on many factors, despite this outcome it is the most commonly performed obstetric procedure worldwide.^{27,28}

According to WHO secondary analysis study on unmet need for induction of labor, African rates of induction of labor are still very far from the expected, averaging 4.4% and 60–80.2% unmet need for labor induction.^{29,30}

Although there is no commonly accepted definition of “failed labor induction.” the current practice acknowledges that “allowing at least 12–18 h of latent labor before diagnosing a failed induction may reduce the risk of cesarean delivery”, Options of management following failed induction of labor include a further attempt to induce labor after consultation with the patient or performing a caesarean section, Ethiopian national guideline for induction recommends Cesarean section only after declared failed induction.³¹

Although induction of labor is a daily practice at public and private health institutions in Ethiopia, including the study area, there is a limitation in undertaking a study on prevalence, outcomes and associated factors of labor induction. Most of the studies concentrated on the success or failure rate of labor induction as a sole outcome, despite abundant literature on various outcomes.³²

Indications and contraindications for induction of labour

Medical and obstetric indications —

Delivery before the onset of spontaneous labor is indicated when the maternal/fetal risks associated with continuing the pregnancy are thought to be at least as great as the maternal/fetal/newborn risks associated with delivery. The risk of continuing the pregnancy is influenced primarily by the severity of the maternal/fetal condition and the risk of delivery is influenced primarily by the gestational age (ie, newborn risks from early birth). The relative risk rarely can be determined with precision. When delivery before the onset of spontaneous labor is desired, induction

of labor and cesarean birth are the only available options. Induction is generally preferred when there are no contraindications to labor and vaginal birth, given the increased maternal risks associated with cesarean birth.³³

Examples of some common conditions where induction is often medically/obstetrically indicated include, but are not limited to, the following:

- Post term pregnancy
- Prelabor rupture of membranes
- Hypertensive disorders – Preeclampsia; eclampsia; HELLP syndrome (hemolysis, elevated liver enzymes, low platelets); gestational hypertension; chronic hypertension
- Diabetes
- Fetal growth restriction
- Twins
- Chorioamnionitis
- Placental abruption
- Oligohydramnios
- Intrahepatic cholestasis of pregnancy
- Alloimmunization with fetal anemia
- Fetal demise

Contraindications —

In each of the following settings, there is general consensus that the maternal/fetal risks associated with labor and vaginal birth, and therefore induction, are greater than the risks associated with cesarean birth; therefore, induction of labor is contraindicated.³³

- Prior classical or other high-risk cesarean incision
- Prior uterine rupture
- Prior extensive complete transmural uterine incision
- Active genital herpes simplex infection
- Placenta previa or vasa previa
- Umbilical cord prolapse or persistent funic presentation
- Transverse fetal lie
- Invasive cervical cancer
- Category III fetal heart rate tracing

Risk-reducing induction —

In the past, induction of labor in low-risk patients at 39 weeks was called "elective"; however, we and others now advocate a terminology change to risk-reducing induction (also called "prophylactic induction" or "induction at 39 weeks"), given evidence that outcomes are at least as good as, if not in some cases better than, expectant management.³³

Preinduction assessment and patient preparation

Checklist — A thorough evaluation of maternal and fetal status is important before undertaking labor induction to make sure the indication is appropriate and to confirm the absence of contraindications to labor or vaginal birth:

- Review the data used to estimate gestational age and date of delivery, given that gestational age is a factor that is considered in timing of induction.
- Determine fetal presentation.
- Estimate fetal weight, given the risks associated with a small or large for gestational age birth weight.

- Perform a cervical examination to decide whether a cervical ripening agent is indicated.
- Review the fetal heart rate pattern to confirm that the use of ripening agents or oxytocin is not contraindicated.

Patient preparation and laboratory tests —

Patient preparation and laboratory tests are generally the same as in patients in spontaneous labor (which includes a review for risk factors for problems that may develop during labor and birth [eg, past history of shoulder dystocia, postpartum hemorrhage]). In addition to standard preparation,

- The indications for and alternatives to induction, planned drugs and procedures including side effects and complications, and the possibility of cesarean birth should be discussed.
- A ripening process is generally employed prior to administering oxytocin in patients with an unfavorable cervix to shorten the duration of labor. Procedures to promote cervical ripening, especially administration of prostaglandins, may initiate labor and obviate the need for oxytocin.

Assessing the chance of a successful induction

Clinical assessment — The likelihood that induction will result in vaginal birth depends on both cervical and noncervical factors.

- A favorable cervix is associated with a shorter duration of induction and higher likelihood of vaginal birth whereas the converse is true when the cervix is unfavorable. However, it should be noted that an unfavorable cervix does not mean that avoiding labor induction and managing the patient expectantly

will result in a higher chance of vaginal birth; patients with unfavorable cervixes are still at increased risk for cesarean birth with expectant management, and the ARRIVE trial demonstrated that the cesarean birth rate was lower with induction regardless of cervical status.³³

- Noncervical factors associated with a higher chance of successful induction (as well as with higher chance of vaginal birth after spontaneous labor) include:
 - Multiparity
 - Ruptured membranes
 - Lower body mass index (BMI)
 - Taller height
 - Lower estimated fetal weight
 - Absence of comorbidities associated with placental insufficiency (eg, preeclampsia)

Bishop score —

The Bishop score is the cervical assessment system most commonly used in clinical practice in the United States. Despite its limitations, it appears to be as, or more, predictive of successful induction than fetal fibronectin or sonographic measurement of cervical length. Cervical scoring systems other than the Bishop score exist but are rarely used for predicting labor outcome (eg, Fields system; Burnett, Caldor, and Friedman modifications of the Bishop system).

The Bishop score is based on the station of the presenting part and four cervical characteristics: dilation, effacement, consistency, and position. Cervical dilation is considered to be the most important of the five scoring elements.

There is no universally accepted threshold for a favorable or unfavorable score. Higher Bishop scores are associated with a higher chance of vaginal birth, while lower Bishop scores have been associated with a higher chance of cesarean birth. Using the Bishop scoring system, most obstetricians consider a score ≥ 6 as favorable and a score ≤ 3 as unfavorable; scores of 4 or 5 are in a gray zone. If the cervix is favorable, oxytocin is administered without cervical ripening. If the cervix is unfavorable, cervical ripening is recommended.

Of note, a simplified Bishop scoring system appears to be as predictive as the original system. In a cohort of over 5400 nulliparas undergoing labor induction at term, only dilation, station, and effacement, which represent three of the original five characteristics comprising the Bishop score, were significantly associated with vaginal birth. For predicting successful labor induction (defined as achieving vaginal birth), a simplified Bishop score using these three components had similar or better positive predictive value (87.7 versus 87.0 percent), negative predictive value (31.3 versus 29.8 percent), positive likelihood ratio (2.3 versus 2.2), and correct classification rate (51.0 versus 47.3 percent) compared with the conventional Bishop score.³³

Non-prognostic factors

- The time of day when induction is started does not appear to be an important independent factor in success.
- Early administration of neuraxial analgesia does not appear to lower the chance of vaginal birth.³³

Table 1: Bishop scoring system³³

	0	1	2	3
Dilation, cm	Closed	1 to 2	3 to 4	≥5 to 6
Effacement, %	0 to 30	40 to 50	60 to 70	≥80
Station*	-3	-2	-1, 0	+1, +2
Cervical consistency	Firm	Medium	Soft	
Position of the cervix	Posterior	Midposition	Anterior	

Methods for induction of labour

Induction of labour (IOL) involves artificially stimulating the onset of labour through chemical and/or mechanical methods, with the aim of achieving a vaginal delivery, prior to the onset of spontaneous labour.³⁴

- Approximately 33.0% of deliveries in the United Kingdom (UK) in 2019–20 were induced, whereas data from the Centres for Disease Control and Prevention demonstrated that 29.4% of deliveries in the United States (US) in 2019 were induced. These figures have increased over the last decade where in the UK, only one in five women had IOL in 2009–10.³⁴
- Induction of labour is offered when continuing with the pregnancy confers more risks to the mother and/or the foetus than delivery. There are various clinical indications which support IOL including maternal diabetes, preeclampsia and hypertension, as well as foetal growth restriction, to name a few.³⁴
- One of the key indications for IOL is to prevent prolonged pregnancy which has been shown to be associated with increased perinatal morbidity and mortality.³⁴

- Data from the Cochrane Database suggest IOL at or beyond 37 weeks' gestation in 'low-risk' pregnancies associates with a reduction in perinatal deaths, stillbirths, and neonatal intensive care admissions.³⁴
- Additionally, there is a modest reduction in caesarean section rates in the induction of labour group compared to expectant management, with no evidence of differences in the rate of instrumental deliveries.³⁴
- The National Institute for Health and Care Excellence (NICE) in the UK as well as the Society of Obstetricians and Gynaecologists of Canada suggest that women with 'uncomplicated pregnancies should usually be offered induction of labour between 41 +0 and 42 +0 weeks'.³⁴
- Regular antenatal assessments with twice-a-week amniotic fluid volume measurements and 'nonstress test' with cardiotocography should be offered to women who choose to delay induction.³⁴
- The American College of Obstetrics and Gynaecology (ACOG), on the other hand, have suggested IOL may be considered at 41 +0 to 42 +0 weeks' gestation and should be recommended beyond 42 +0 weeks' gestation.³⁴
- Given the global increase in obese pregnant women, it is crucial to have clear guidance on IOL in this group of women. However, there remains a lack of consensus in optimum gestation for IOL and choice of induction agents. Nevertheless, this chapter aims to collate the available information to aid in decision-making with respect to induction of labour in obese women.³⁴

Indications of induction of labour

1. Postdates pregnancy³⁴

- Denison et al. have demonstrated that maternal obesity is associated with a reduced likelihood of spontaneous onset of labour and greater risk of postdates pregnancies.
- Maternal obesity during pregnancy is also associated with an increased risk of complications including maternal diabetes and preeclampsia, which may in themselves warrant earlier delivery.
- This is reflected in an increased risk of induction of labour among obese pregnancies (odds ratio 1.70, 99% confidence interval 1.64–1.76).
- In general, IOL among obese pregnant women with prolonged pregnancy is considered safe with no difference in Apgar scores and cord blood pH between obese and lean pregnancies.
- However, it has also been reported that the likelihood of vaginal delivery following IOL in obese pregnant women is reduced when compared to those with normal body weight (rate of unassisted vaginal delivery in obese vs lean pregnancies, 55.0% vs 57.9%).
- Obese pregnancies are associated with an increased risk of delivery by caesarean section (rate of caesarean section delivery in obese vs lean pregnancies, 28.5% vs 18.9%, $P < .001$) and prolonged second stage of labour.
- Interestingly, when compared to IOL, elective caesarean sections in obese pregnant women have not been shown to improve maternal and neonatal outcomes, further supporting IOL as a safe and reasonable intervention for obese pregnancies.

2. Diabetes, including gestational diabetes and preexisting diabetes³⁴

- Both gestational diabetes mellitus (GDM) and preexisting diabetes is more common among obese pregnant women, and associated with an increased risk of maternal and foetal morbidity and mortality.³⁴
- Delivery between before 39 +0 weeks' gestation is recommended in women with preexisting type 1 or 2 diabetes, whereas those with uncomplicated GDM should be offered delivery before 40 +0 weeks' gestation.
- Both NICE and ACOG have suggested that the mode of delivery should be determined by maternal diabetic control and foetal well-being.

3. Hypertensive disorders of pregnancy, including preeclampsia³⁴

- Maternal obesity is associated with a higher incidence of preexisting hypertensive disorders, pregnancy-induced hypertension and preeclampsia.
- Early delivery is commonly indicated in cases where there is evidence of maternal and/or foetal deterioration.
- Further, results from the HYPITAT trial indicated that induction of labour in women with pregnancy-induced hypertension and mild preeclampsia was associated with a lower composite risk for poor maternal outcome secondary to progression of the disease.
- While this study did not perform a subgroup analysis for obese pregnant women, there is evidence suggesting that obese pregnant women with preeclampsia are less likely to progress to a vaginal delivery following IOL.
- The decision with regards to mode of delivery in this cohort of patients therefore requires a personalised and multidisciplinary approach.

4. Foetal macrosomia³⁴

- While maternal obesity, with or without concurrent diabetes, associates with an increased risk of foetal macrosomia and shoulder dystocia.
- However, prediction of large-for-gestational age or foetal macrosomia during the antenatal period remains challenging due to inaccuracies with symphyseal-fundal height measurements in obese pregnant women.
- Ultrasound assessment of estimated foetal weight during the third trimester is also subject to a degree of variability and increased maternal adiposity can impact on the quality of the images – thus resulting in inaccurate measurements.
- A Cochrane review on induction of labour in pregnancies with suspected foetal macrosomia did not demonstrate a clear role of IOL at or near term in reducing the risk of brachial plexus injuries.
- Therefore, in the absence of other risk factors, IOL for suspected foetal macrosomia in obese pregnancies should be considered with caution.

5. Elective induction of labour³⁴

- The risk of stillbirth is greater in pregnancies affected by maternal obesity and there appears to be a linear relationship between risk of stillbirth and advancing gestation in obese pregnancies.
- Crucially, there is evidence that elective IOL in obese pregnancies may improve neonatal outcomes without increasing maternal morbidity.
- Indeed, the Royal College of Obstetricians and Gynaecologists (RCOG) has recommended that while maternal obesity in itself is not an indication for elective IOL, it should still be considered and discussed on an individual basis.

Counselling for induction of labour

1. Gestation at the time of IOL

- In the absence of maternal and/or foetal complications, consider offering elective IOL at term.
- Pregnancies complicated by diabetes

2. Assessment prior to IOL

- Confirm gestation and presence of any risk factors (e.g. diabetes or hypertensive disorders of pregnancy) which may influence timing of IOL.
- Consider referral to Anaesthetic team – the RCOG recommends that women with BMI ≥ 40 kg/m² should be referred to the anaesthetic team for early discussion of options for analgesia and to assess and plan for potential challenges with regional and general anaesthesia.
- Foetal lie and presentation – this may be challenging with increased maternal adiposity and therefore confirmation of presentation with ultrasound may be indicated.
- Cervical assessment – the Bishop scoring system is commonly used to assess the cervix and may influence the choice of induction agent. (table 1)

3. Previous caesarean section

- Individualised care, taking into consideration severity of obesity, parity and previous history of vaginal deliveries, cervical assessment and maternal preference.
- Increased risk of unsuccessful trial of labour in obese pregnant women with previous caesarean section

- Risk of unsuccessful trial of labour in morbidly obese (i.e. BMI ≥ 40 kg/m²) versus those with normal BMI – 39.3% versus 15.2%.
- Successful trial of labour in obese (i.e. BMI ≥ 30 kg/m²) versus those with normal BMI – 54.6% versus 70.5%.
- Risk of uterine scar dehiscence or rupture is increased with maternal obesity (2.1% in morbidly obese pregnancies).
- Risk of neonatal injuries, including brachial plexus injuries, fractures, and lacerations (fivefold increase in risk, 1.1% in morbidly obese pregnancies versus 0.2% in normal weight pregnancies).

4. Foetal monitoring

- Continuous electronic foetal monitoring should be performed following administration of IOL measures. Once there is confirmation of foetal well-being with a normal cardiotocogram, intermittent auscultation is reasonable unless there are indications for continuous electronic foetal monitoring.
- Once active labour is established, continuous electronic foetal monitoring should be offered.
- Palpation of uterine activity and accurate recording of foetal heart using transabdominal probes may be challenging with increased maternal adiposity. Women should be counselled about the possible need for a foetal scalp electrode to monitor foetal heart rate.

5. Home versus inpatient IOL

- Evidence is inconclusive although there is evidence suggesting that there is no difference in maternal and foetal morbidity and mortality in home versus inpatient IOL.

- Outpatient IOL may associate with shorter duration of hospital stay and reduced caesarean section rates. However further studies are required to confirm the validity of these findings, especially in pregnancies complicated by maternal obesity.

Methods of induction of labour

1. All women should be offered a vaginal examination with membrane sweep where possible.

2. Pharmacological methods for cervical ripening:

- Prostaglandin E 2
 - Available in vaginal preparation as a controlled-release pessary, gel or tablet.
 - Controlled-release pessary: 1 dose over 24 hours (maximum).
 - Gel or tablet: usually divided into multiple doses given at 6-hour intervals. NICE guidance recommends maximum of 2 doses.
 - Risk of tachysystole or hyperstimulation.
- Prostaglandin E 1
 - Not recommended for IOL under NICE guidance, unless it was for the use of induction of labour following stillbirth or in the context of a clinical trial.
 - Misoprostol can be used in IOL in viable pregnancies under the SOGC and ACOG guidance and is recognised to have a rapid onset of action. It carries a risk of tachysystole and therefore is not recommended for use in an outpatient setting or in women with a previous Caesarean section due to risk of uterine rupture.
 - In Europe, the use of vaginal misoprostol for IOL was approved in 2013 and Varlas et al. demonstrated that MVI-Misodel is an effective pharmacological

IOL agent in high risk (including postdates pregnancy, hypertension and diabetes) obese pregnant women with no evidence of difference in Caesarean section rates, as well as maternal and neonatal outcomes.

- Consider adjusting prostaglandin (and oxytocin) dose as maternal obesity has been shown to require high doses of induction agents.

3. Mechanical methods:

- Transcervical double-balloon or Foley catheters
 - NICE does not recommend routine use of catheters for IOL. However, there appears to be a renewed interest in this IOL method, particularly in women who have had a previous caesarean section, as it does not directly stimulate uterine contractions, and thus should in theory have a reduced risk of uterine rupture. It may also be a favoured option for outpatient IOL due to lower risk of uterine hyperstimulation.
 - The PROBAAT and PROBAAT-II randomised controlled trial has shown that IOL in an unfavourable cervix with pharmacological methods (prostaglandin, PROBAAT and misoprostol, PROBAAT-II) was not superior to the use of Foley catheter. Additionally, the use of Foley catheters may associate with a lower risk of maternal morbidity.
 - There is evidence supporting the use of intrauterine devices such as transcervical catheters in conjunction with oral misoprostol in obese pregnant women. Kehl et al. have shown that sequential use of the double-balloon catheter followed by oral misoprostol associated with higher rates of vaginal deliveries when compared to oral Misoprostol alone. However, this is a small study with only 400 participants and further studies are required to explore neonatal outcomes and patient experience from this method.

4. Amniotomy:

- NICE guidance does not recommend the use of amniotomy as the primary method for IOL, unless there are contraindications for pharmacological agents.
- Reserved for women with favourable cervix.
- Consider use of oxytocin following amniotomy. There is a lack of consensus about the interval between amniotomy and commencement of the oxytocin infusion, although the SOGC suggests ‘early’ use of oxytocin following amniotomy.

Pharmacologic Methods of Cervical Ripening

Prostaglandins

Administration of PGs results in the dissolution of collagen bundles and an increase in the submucosal water content of the cervix. These changes in cervical connective tissue at term are similar to those observed in early labor. PGs are endogenous compounds found in the myometrium, decidua, and fetal membranes during pregnancy. The chemical precursor is arachidonic acid. PG formulations have been used since they were first synthesized in the laboratory in 1968, and PG analogues were originally given intravenously and orally. Later, local administration of PGs in the vagina or the endocervix became the route of choice because of fewer side effects. Side effects of all PG formulations and routes may include fever, chills, vomiting, and diarrhoea.

The efficacy of locally applied PGs (vaginal or intracervical) for cervical ripening and labor induction has been demonstrated in systematic reviews that included more than 10,000 women.

The various administration vehicles for PG (tablet, gel, and timed-release pessary) appear to be equally efficacious in achieving a vaginal delivery, although differences in time to delivery have been noted. The optimal route, frequency, and dose of PGs of all types and formulations for cervical ripening and labor induction have not been determined. Also, PG formulations of any kind should be avoided as third-trimester cervical ripening agents in women with a prior uterine scar, such as a prior cesarean delivery or myomectomy, because their use has been associated with an increased risk of uterine rupture. 158 Uterine activity and fetal heart rate monitoring are indicated for 0.5 to 2 hours after administration of PGs for cervical ripening and should be maintained as long as regular uterine activity is present. 1 Regular uterine activity is often not clearly defined. However, if the patient is having painful contractions more than two times in 10 minutes, caution should be used when additional doses of PG are being considered.

Prostaglandin E 2

Multiple trials have evaluated the effectiveness of intravaginal PG. 56575960 Rayburn summarized 59 clinical trials comprising 3313 women in which either intracervical or intravaginal prostaglandin E 2 (PGE 2, dinoprostone) was used for cervical ripening before induction of labor. He concluded that local administration of PGE 2 is effective in enhancing cervical effacement and dilation, shortening the induction-to-delivery interval, reducing oxytocin use, and lowering the chance of cesarean delivery for failure to progress when compared to oxytocin alone. These findings were confirmed in a meta-analysis of 44 trials performed worldwide using various PG compounds and dosing regimens. Because no difference in clinical outcomes are apparent when comparing intravaginal or intracervical PGE 2

preparations, vaginal administration has been recommended given its greater ease of administration and patient satisfaction.

Currently two PGE 2 preparations have been approved by the US Food and Drug Administration (FDA) for cervical ripening. 1 Prepidil contains 0.5 mg dinoprostone per 3-g syringe (2.5-mL gel), and is administered intracervically. The dose can be repeated in 6 to 12 hours if cervical change is inadequate and uterine activity is minimal following the first dose. Oxytocin should not be initiated until at least 6 hours after the last dose because of the potential for uterine tachysystole with concurrent oxytocin and PG administration. Cervidil is a vaginal insert that contains 10 mg of dinoprostone in a timed-release formulation. The vaginal insert administers the medication at 0.3 mg/h and may be left in place for up to 12 hours. The insert may be removed with the onset of active labor, rupture of the membranes, or with the development of uterine tachysystole. Per the manufacturer's instructions, oxytocin may be initiated 30 to 60 minutes after removal of the insert. However, these two preparations are relatively expensive and require refrigerated storage because they become unstable at room temperature.

Prostaglandin E 1

Misoprostol is a synthetic PGE 1 analogue available as 100- and 200- μ g tablets. The current FDA-approved use of misoprostol is for the treatment and prevention of peptic ulcer disease related to the chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs). Additionally, the FDA has approved the relabelling of misoprostol, making its use appropriate for cervical ripening and for the induction of labor during pregnancy.

Administration of misoprostol for preinduction cervical ripening is considered a safe and effective use by ACOG. Misoprostol is inexpensive and is stable at room temperature; it can be administered orally or placed vaginally with few systemic side effects. Although not scored, the tablets can be divided to provide 25- or 50- μ g doses.

Pharmacology of Misoprostol:

Misoprostol (15-deoxy-16-hydroxy-16-methyl PGE₁) is a synthetic prostaglandin E₁ analogue. It was developed for the prevention and treatment of peptic ulcers because of its gastric acid anti-secretory properties and its various mucosal protective properties.

Structure and chemical properties:

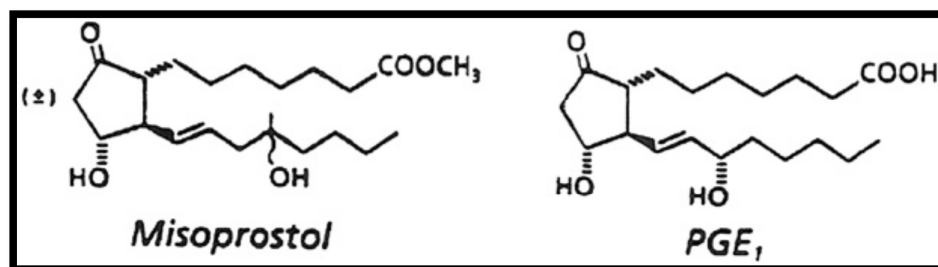


Figure 1 The structure of misoprostol and naturally occurring prostaglandin (PGE₁).

Fig.1 shows the structures of misoprostol and naturally occurring prostaglandin E₁. The naturally occurring prostaglandin E series was discovered to inhibit gastric acid secretion in 1967 by Robert et al.³⁶ However, they have three drawbacks which limited their clinical uses. These drawbacks were: 1) rapid metabolism resulting in a lack of oral activity and a short duration of action when given parenterally 2) numerous side effects and 3) chemical instability leading to a short shelf life.

Misoprostol differs structurally from prostaglandin E by the presence of a methyl ester at C-1, a methyl group at C-16 and a hydroxyl group at C-16 rather than C-15. The methyl ester at C-1 increases the anti-secretory potency and duration of action of misoprostol, whilst the movement of the hydroxyl group from C-15 to C-16 and the addition of a methyl group at C-16 improves oral activity, increases the duration of action, and improves the safety profile of the drug.

Pharmacokinetics of various routes of administration of Misoprostol:

Misoprostol tablets were developed to be used orally. Other routes of administration, however, including vaginal, sublingual, buccal and rectal, have also been used extensively in obstetric and gynaecological applications. Over the past decade there have been a number of studies looking at the pharmacokinetic profile of various routes of administration of misoprostol. Three pharmacokinetic properties, the peak concentration, time to peak concentration and the area under the serum concentration versus time curve were studied.³⁷⁻⁴⁰ The time to peak concentration (T_{max}) represents how rapidly the drug can be absorbed; the peak concentration (C_{max}) reflects how well the drug is being absorbed while the area under the serum concentration versus time curve (AUC, equivalent to bioavailability) denotes the total exposure to the drug.

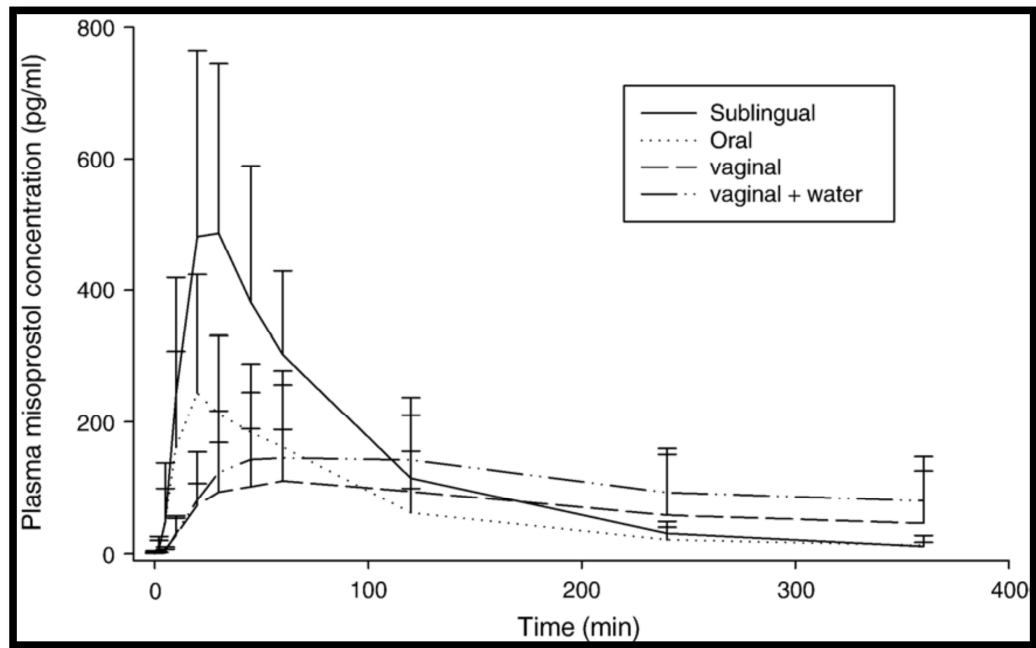


Figure 2: Mean plasma concentrations of misoprostol acid over time (arrow bars=1 SD). [Tang. Pharmacokinetics of different routes of administration of misoprostol.

Hum Reprod 2002. Reproduced by permission of Oxford University Press].

Oral Route- Early studies concentrated on pharmacokinetic properties after oral administration. After oral administration, misoprostol is rapidly and almost completely absorbed from the gastrointestinal tract. However, the drug undergoes extensive and rapid first-pass metabolism (de-esterification) to form misoprostol acid. Following a single dose of 400 μg oral misoprostol, the plasma misoprostol level increases rapidly and peaks at about 30 minutes (fig.2), declines rapidly by 120 minutes and remains low thereafter.³⁷⁻⁴⁰

Vaginal Route- It was found in clinical studies that vaginal administration was more effective than oral route in medical abortion.^{42,43} Zeiman et al performed the first pharmacokinetic study comparing oral and vaginal routes of administration.⁴⁴ In contrast to the oral route, the plasma concentration increases gradually after vaginal

administration, reaching its maximum level after 70-80 minutes before slowly declining with detectable drug levels still present after 6 hours. Although, the peak concentration after oral route is higher than for vaginal route of administration, the 'area under the curve' is higher when given vaginally. The greater bioavailability of vaginal misoprostol may help to explain why it is more effective in medical abortion. It has been shown that the coefficient of variation of the AUC after vaginal administration is greater than that after oral administration. This means that the vaginal absorption of misoprostol is inconsistent. In clinical practice, remnants of tablets sometimes seen many hours after vaginal administration, indicating that the absorption is variable and incomplete. This may be due to the variation between women in the amount and PH of the vaginal discharge. Variation in the amount of bleeding during medical abortion may also affect the absorption of misoprostol through the vaginal mucosa. Numerous attempts have been made to improve the absorption of vaginal misoprostol. The addition of water to the misoprostol tablets is a common practice. However, this has been shown not to improve the bioavailability of vaginal misoprostol.³⁸

Sublingual Route: Recently, sublingual administration of misoprostol has been studied for medical abortion and cervical priming. The misoprostol tablet is very soluble and can be dissolved in 20 minutes when it is put under the tongue. From the study, it is found that sublingual misoprostol has the shortest time to peak concentration, the highest peak concentration and the greatest bioavailability when compared to other routes.³⁸ [fig.2]

The peak concentration is achieved about 30 minutes after sublingual and oral routes, whereas following vaginal route, it takes about 75 minutes.³⁸ Therefore, it appears that the sublingual and oral routes have the quickest onset of action. After 400

µg of misoprostol, a sublingual dose achieves a higher peak concentration than that of oral and vaginal routes. This is due to rapid absorption through the sublingual mucosa as well as the avoidance of the first-pass metabolism via the liver. The abundant blood supply under the tongue and the relatively neutral PH in the buccal cavity may be contributing factors.

Buccal Route: The drug is placed between the teeth and the cheek and allowed to be absorbed through the buccal mucosa. After buccal administration, the T_{max} is 75 minutes which is similar to that for vaginal administration, but the AUC of buccal administration is just half that of the vaginal administration. In another study comparing buccal to sublingual administration has also shown that the AUC of sublingual misoprostol is 4 times that of buccal administration.⁴⁵

Rectal Route: This route has been recently studied for the management of PPH and less commonly for other applications. The shape of the absorption curve after rectal administration is similar to that of vaginal administration but its AUC is only 1/3 that of vaginal administration. The mean T_{max} after rectal route is 45-60 minutes.⁴⁶

By conclusion of above all the pharmacokinetics studies, the sublingual route has the shortest T_{max}, which is useful for clinical applications that require a fast onset of clinical action, such as PPH or cervical priming. Vaginal route has high bioavailability and sustained serum level, is useful for indications that require a longer time for its action like medical abortion. The absorption kinetics also explain why some routes are associated with a higher incidence of side effects. Sublingual route which gives the highest C_{max}, is associated with highest incidence of side effects when compared to other routes.

Misoprostol is a safe and well tolerated drug. Pre-clinical toxicological studies indicate a safety margin of at least 500-1000-fold between lethal doses in animals and therapeutic doses in humans.⁴⁷ No clinically significant adverse haematological, endocrine, biochemical, immunological, respiratory, ophthalmic, platelet or cardiovascular effects have been found with misoprostol. Diarrhoea is the major adverse reaction that has been reported consistently with misoprostol, but it is usually mild and self-limiting. Nausea and vomiting may also occur and will resolve in 2 to 6 hours. Fever and chills have also been reported and are common following high doses in the third trimester or immediate postpartum period. The typical situation in which this is seen is when misoprostol is used for the prevention or treatment of PPH.⁴⁸

Some women found an unpleasant taste when it is taken sublingually or buccally. A sense of numbness over the mouth and throat has also been reported when it is taken sublingually.

The toxic dose of misoprostol is unknown, but it has been considered to be a very safe drug. However, a recent case report has identified a woman who died of multi-organ failure following an overdose of misoprostol (60 tablets over 2 days).⁴⁹

Although, oxytocin is the drug of choice for PPH prevention and treatment, AMTSL with use of conventional oxytocic agents is not practical in low resource settings like in developing countries because of the need for proper storage, protection from light, need for refrigeration, parenteral administration by skilled personnel and high cost. Sublingual misoprostol because of its cost effectiveness, thermostability, easy administration, long shelf life without special storage conditions is a promising drug in AMTSL implementation.⁵⁰

Pharmacology of Mifepristone

Mifepristone is a synthetic steroid. It is a medication most commonly used for medically induced abortions. Mifepristone can also be used in the management and treatment of Cushing's syndrome and uterine leiomyomas. At low doses, mifepristone blocks progesterone by competitively binding its intracellular receptor. At high doses, mifepristone blocks cortisol at the glucocorticoid receptor, thus simultaneously increasing the amount of circulating cortisol, which controls hyperglycemia in patients with Cushing syndrome. The significant adverse reactions to mifepristone include bacterial infections and prolonged, heavy menstrual bleeding. Mifepristone is contraindicated in patients with: an ectopic pregnancy, hypersensitivity to prostaglandins, undiagnosed renal masses, concurrent IUD use, hemorrhagic disorders, and severe anemia. This activity will highlight the mechanism of action, adverse event profile, and other key factors (e.g., dosing, pharmacodynamics, pharmacokinetics, monitoring, and relevant interactions of mifepristone) that pertain to the healthcare team when treating patients with mifepristone.⁵¹

Indications

Mifepristone has two main FDA-approved indications. These are pregnancy termination combined with misoprostol through ten weeks gestation and the management and treatment of hyperglycemia in patients exhibiting signs of Cushing syndrome. In addition to the above indications, mifepristone has shown efficacy with off-label uses when it comes to postcoital emergency contraception, cervical maturation, and adjunct therapy for uterine leiomyomas.⁵¹

Mechanism of Action

Mifepristone works by being an antagonist of glucocorticoid and progesterone receptors. At low doses, mifepristone works by being a selective antagonist of progesterone. It does so by binding to the intracellular progesterone receptor. At high doses, mifepristone blocks cortisol at the glucocorticoid receptor. This action causes an effect on the hypothalamic-pituitary-adrenal axis, leading to an increase in circulating cortisol, thus controlling hyperglycemia in some patients. Mifepristone has a higher affinity for the glucocorticoid II receptor than it does for the glucocorticoid I receptor.

In the instance of pregnancy termination, mifepristone works by interrupting progesterone. Progesterone is the primary hormone in preparing the endometrium for implantation as well as sensitizing the body to the effects of prostaglandins by increasing their synthesis and decreasing their metabolism. The increase in prostaglandins results in menstrual bleeding, disruption of the endometrium, and then termination.⁵¹

Administration

In general, mifepristone is available as an oral tablet in 200 mg and 300 mg preparations.

For all the indications listed above, the administration of mifepristone is via oral out. For pregnancy termination, mifepristone dosing should be a single dose of 200 mg. For the management and treatment of hyperglycemia in patients with Cushing syndrome, an initial dose of 300 mg should be given orally once daily with a meal. That dose may be increased by 300 mg every two-four week up to a maximum dose of 1200 mg per day. For emergent postcoital contraception, 600 mg should be

given orally in a single dose within seventy-two hours of intercourse. In the treatment of uterine leiomyomas, 25 to 50 mg once daily orally can help reduce the size of the fibroids.

In patients with hepatic impairment, additional administration instructions are necessary for managing hyperglycemia with mifepristone. For these patients, the dosing should not exceed 600 mg orally per day. In patients with renal impairment with creatinine clearance of under ninety milliliters per minute, the dose should not exceed 600 mg orally per day.⁵¹

Adverse Effects

Severe reactions include fetal death, anaphylactic reactions, toxic epidermal necrolysis, angioedema, and teratogenesis.

Moderate reactions may present as hypokalemia, peripheral edema, hypertension, dyspnea, constipation, hypoglycemia, vaginal bleeding, uterine contractions, stomatitis, hot flashes, endometrial hyperplasia, anemia, adrenocortical insufficiency, palpitations, and hypotension.

Mild reactions that may occur include nausea, abdominal pain, fever, vomiting, fatigue, headache, diarrhoea, dizziness, sinusitis, pharyngitis, GERD, malaise, insomnia, maculopapular rash, pruritis, pelvic pain, chills, menstrual irregularity, emotional lability, and syncope.⁵¹

Contraindications

When using mifepristone to terminate a pregnancy or conception, caution is necessary to test out the patient populations with contraindications to mifepristone. Patients who have had a hypersensitivity reaction to mifepristone in the past or to

prostaglandin therapy should not have mifepristone therapy. Hypersensitivity reactions include symptoms of anaphylaxis, angioedema, rash, hives, and pruritis.

The use of mifepristone in Cushing syndrome patients is contraindicated in patients taking simvastatin, lovastatin, and CYP3A substrates (i.e., cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus, and tacrolimus). Additionally, mifepristone is contraindicated in pregnant patients for the control of hyperglycemia. If the patient has a history of unexplained vaginal bleeding, endometrial cancer, or endometrial hyperplasia with signs of atypia, they should not receive mifepristone. Physicians need to be watchful for symptoms of abdominal pain, infection, sepsis, and vaginal bleeding after starting this medication. If these symptoms develop, the clinician should stop mifepristone immediately.⁵¹

Monitoring

After administering mifepristone, several adverse reactions require monitoring, one of which being severe bacterial infections post medical abortion or post dilatation and curettage procedure where the use of mifepristone was indicated. There is no causal relationship between the drug and developing an infection, but they can occur. Before prescribing mifepristone, the patient should understand the risks, signs to look for, and a plan of action in the event they need to seek help. Signs to look out for include sustained fever, severe abdominal pain, heavy bleeding: syncope, or general malaise lasting more than 24 hours after taking the medication. If a bacterial infection occurs, there is a high possibility that *Clostridium sordellii*, which can present atypically.⁵¹

Prolonged, heavy bleeding after taking mifepristone is a possibility based on the mechanism of action of the drug. Mifepristone promotes endometrial proliferation,

leading to endometrial thickening and heavier vaginal bleeding. Bleeding is expected on average for 9-16 days post-pregnancy termination. The manufacturer describes excessive bleeding as soaking through 2 thick pads every hour. If excessive bleeding occurs, it could point to an incomplete abortion or other complications. In these instances, monitoring for hypovolemic shock becomes important.⁵¹

When using mifepristone in the management of Cushing syndrome patients, it is crucial to consider the effects on the HPA axis. This treatment can lead to adrenal insufficiency as a result of persistently elevated cortisol levels. Due to this, the cortisol levels should not serve as a monitoring parameter. Clinically, watch for signs of fatigue, hypoglycemia, hypotension, nausea, or weakness. If the clinician observes these, discontinue mifepristone and administer high-dose steroids. Once resolved, mifepristone may be started back at a lower dose. Hypokalemia needs to be monitored in these patients as well. Of note, patients receiving treatment for Cushing syndrome are at higher risk for developing opportunistic infections such as *Pneumocystis jirovecii* pneumonia.⁵¹

In general, mifepristone can prolong the QTc interval, and its use merits caution in combination with other drugs that also prolong the QT interval.

Toxicity

Mifepristone is metabolized in the liver by CYP3A4; thus, medications that are CYP3A4 inhibitors can result in higher concentrations of mifepristone in the patient. Also, for patients taking multiple doses of mifepristone, for instance, in managing hyperglycemia in Cushing syndrome, the half-life of the medication is reported to be around 85 hours. During this time, the significant symptoms to watch for are cardiogenic. Hypokalemia is very common due to the effects of cortisol on

unopposed mineralocorticoid receptors. To avoid problems with mifepristone toxicity and side effects, the suggestion is to titrate the dosages gradually. It is essential to have follow-up and monitoring of the patient during the dosage escalation process. ⁵¹

Similar studies conducted in the past

Giacalone PL et al⁵² in 1998 conducted the study with the objective to determine the efficacy and safety of mifepristone for cervical ripening in post-term pregnancies. Women with post-term pregnancies and Bishop scores less than 6 were assigned randomly to mifepristone (41 patients) or placebo (42 patients). Mifepristone was given orally in a dose of 400 mg. Efficacy was assessed by change in the Bishop score within 48 hours after treatment; a score of 6 or greater was considered a “strict” success. An “extended” success rate was defined, including all patients with scores of at least 6 or those who delivered within 48 hours of treatment. Antenatal safety was assessed by fetal heart rate testing before and throughout labor. Neonatal safety was assessed by Apgar score, arterial or venous pH of cord blood, and blood glucose level during the first 48 hours. Analysis used Student t test for continuous variables, Kruskal-Wallis test for ordinal data, and x² for categoric variables. Strict success was achieved in 10 of 18 mifepristone patients (55%) evaluated for Bishop score on day 2 versus 8 of 29 placebo patients (27.5%) (P 5 .004). Extended success was achieved in 33 mifepristone patients (80.5%) and 21 placebo patients (50.0%) (P 5 .004). There were no statistical differences with regard to number of cesareans or fetal and neonatal safety. The authors here concluded that Mifepristone proved effective for cervical ripening and reduced the time to delivery compared with placebo, but it did not improve the rate of cesarean. Our study did not include enough pregnancies to reach conclusions about fetal or neonatal safety.

Berkane N et al⁵³ in 2005 conducted the study with the objective to determine the efficacy of mifepristone for ripening the cervix and inducing labor in term pregnancies. In a double-blind placebo-controlled dose-finding study, 346 women received 50, 100, 200, 400, or 600 mg of mifepristone or placebo. The main endpoint for efficacy was the number of patients in whom labor occurred between 12 and 45 and 54 hours after treatment or who had a Bishop score 6 or greater. Maternal and fetal tolerability was also studied. No significant efficacy was observed whatever the dose of mifepristone. Mifepristone was well tolerated by the mother and fetus. They concluded that Mifepristone, at doses up to 600 mg, does not induce labor within 54 hours in patients with unfavourable cervical status.

McGill J et al⁵⁴ in 2007 conducted the study with the objective to assess the ability of mifepristone to prime the cervix adequately and induce labor in pregnant women at term; and when mifepristone alone proves insufficient, to determine whether oral misoprostol taken 48 h following mifepristone administration is effective in inducing labor. Methods: In this prospective study 50 pregnant women at term with an unfavorable cervix were given 400 mg of mifepristone orally and allowed to return home. If labor did not start within 48 h, the women were admitted and induction was continued with 50 µg of misoprostol, a prostaglandin (PG) E1 analogue, taken orally every 4 h. The 50 controls, who were matched prospectively for parity and pregnancy duration, underwent labor induction according to the routine administration of 3-mg tablets of PGE2 vaginally. Results: In the study group, 66% of the women entered labor spontaneously or had a sufficiently ripened cervix within 48 h of taking mifepristone. However, there was no difference in time between prostaglandin administration and delivery between the control group and the 34% of women who required misoprostol in the study group. In the study group, the cesarean section rate

was significantly lower among the women whose labor was induced with mifepristone alone than among those who required misoprostol. There were no differences overall in obstetric or neonatal outcomes between the study and control groups. So they concluded here that in this pilot sample, 400 mg of mifepristone was effective in inducing cervical changes and labor. Although there were no adverse effects using oral misoprostol in combination with mifepristone, labor was more difficult to induce in the women who did not respond to mifepristone alone, and these women had a higher operative delivery rate.

Ashtekar Archana et al⁵⁵ in 2014 conducted the study with the objective to compare the efficacy, safety and fetomaternal outcome of Misoprostol as cervical ripening and labor inducing agent versus Mifepristone and Misoprostol. The study also aims to observe the improvement in pre induction Bishop's score, proportion of patients going in labor, to study induction–delivery interval. It is randomized prospective studies conducted on 100 women. Women were randomized in group A and in group B of 50 patients in each group. Group A received tab Mifepristone 200 mg orally on day 1 followed by tablet Misoprostol 25 mcg after 48 hours and continued 4 hrly till patient went in active labor with maximum four tablets and group B patients received tablet Misoprostol 25mcg and continued 25mcg 4hrly till patient went in active labor. The study demonstrated significant efficacy of tablet Mifepristone for cervical ripening and induction of labor as pre induction Bishop's score was improved. 32% patients went into labor only with tablet Mifepristone. The mean induction-delivery interval was 9.5 hrs in Group A and 11.78 hrs in Group B, 40% patients delivered by cesarean section in group A but it was not associated with any differences in final neonatal outcome in both the groups. Uterine hyper stimulation was present in 42% patients in group A as compared to only 20% patients in group B. Fetal distress was present in

38% of patients in group A as compared to 18% patients in group B. No any difference in final neonatal outcome was observed in both the groups. So they concluded that Mifepristone pretreatment is more efficacious and significantly shortens the induction-delivery interval and it has got dual role as a cervical ripening and labor inducing agent.

Yelikar K et al⁵⁶ in 2015 conducted the study with the objective to study the safety and efficacy of oral mifepristone in pre-induction cervical ripening and induction of labour in prolonged pregnancy. Method(S) This is a single blind randomized control trial. 100 women with prolonged pregnancy beyond 40 weeks and Bishop score ≥ 6 were recruited, and randomly allocated into two groups. Women who received Tab. Mifepristone 200 mg orally were assigned in Study Group (n = 50) and who received placebo orally were assigned in Control Group (n = 50) At the end of 24 h, change in the Bishop's score was assessed and Tab. Misoprostol 25 μ g was administered intravaginally every 4 h, maximum 6 doses for induction/augmentation of labour. Analysis regarding safety and efficacy of the drug was done with regards to maternal and perinatal outcome. Result(S) Among 100 subjects, 50 received mifepristone and 50 received placebo. Mean induction to delivery interval was $1,907 \pm 368.4$ min for Study Group versus $2,079 \pm 231.6$ min for Control Group. The improvement in mean Bishop score was 5.0408 ± 1.90 for Study Group compared with 3.26 ± 1.15 was for Control Group after 24 h. Mean dose of misoprostol in Study Group was 40 ± 27.2 , while the same in Control Group was 52 ± 19.46 . Eight (16 %) women in Study Group and two (4 %) women in Control Group delivered vaginally within 24 h without any need of augmentation. There were 6 (12 %) cesareans and 2 (4 %) instrumental deliveries in Study Group and 8 (16 %) cesareans and 5 (10 %) instrumental deliveries in the Control Group. There was no statistically significant

difference in perinatal outcomes between two groups. Conclusion(S) Mifepristone had a modest effect on cervical ripening when given 24 h prior to labour induction and appearing to reduce need for misoprostol compared with placebo. **Sharma R et al⁵⁷ in 2018** conducted the study with the objective to compare the improvement in pre-induction Bishop's score, proportion of patients going in labor and induction–delivery interval after using the Misoprostol versus Mifepristone and Misoprostol as cervical ripening and labor inducing agent. It is retrospective comparative study conducted on 110 women. Women were randomized in group A and in group B of 55 patients in each group. Group A received tab Mifepristone 200 mg orally on day 1 followed by Misoprostol 25 ug after 48 hours and continued 6-hourly till maximum four tablets and group B patients received tablet Misoprostol 25ug and continued 25ug 6hrly maximum 4 doses. Women observed for improvement in Bishop's score, induction-delivery interval and requirement of subsequent doses of Misoprostol. Present study concluded that tablet Mifepristone is an efficient cervical ripening and inducing agent of labor as pre-induction Bishop's score was improved. 36.4% patients went into labor only with tablet Mifepristone. The mean induction-delivery interval was, 19 ± 12.2 hrs in Group 1 as compare to 13.1 ± 13.0 hrs in Group 2. Mean Bishop's score observed in Group 1 were 2.5 ± 1.78 and 1.67 ± 1.25 in Group 2. It was observed that there was significant improvement in the Bishop's score after giving Mifepristone to the patients; mean Bishop's 24hrs after mifepristone were 4.03 ± 1.80 . Repeated dose of Misoprostol required in Group 1 was observed to be higher than group 2 as shown in table 8. Mean misoprostol doses required in group 1 was 2.56 ± 1.15 as compared to 1.71 ± 1.58 in group 2. Mifepristone with Misoprostol reduce the induction delivery interval and more potent in combination for induction of labour as compared to Misoprostol alone

Dr. Shweta Sharma et al⁵⁷ in 2018 conducted the study with the objective to determine whether the combination of mifepristone and misoprostol is more effective than misoprostol alone in causing labour to begin in women who have had intrauterine foetal demise. The study was a parallel group superiority trial that was randomized, double-blind, and placebo controlled. Oral administration of 200 mg of mifepristone or matching placebo tablets was given to 110 pregnant women who had previously suffered foetal mortality occurring at or after 20 weeks of gestation, according to a computer-generated random number sequence. Women in both groups were given misoprostol vaginally 36 to 48 hours later. The primary outcomes that were examined were the induction-delivery interval and the fetal-placental delivery rate within 24 hours of starting the first dosage of misoprostol without any further interventions. The success rate of a woman's birth was significantly higher in the group that got mifepristone in addition to misoprostol (71.2%) than in the group that received just misoprostol (71.2%). When misoprostol was used in conjunction with mifepristone, the average induction-delivery interval was 9.8 hours with a standard deviation of 4.4, compared to 16.3 hours with a standard variation of 5.7, and the difference was statistically significant ($P < 0.001$). When compared to using misoprostol alone, a combination of mifepristone and misoprostol greatly increased the success rate of deliveries and decreased the time between induction and delivery for women who had suffered foetal death.

MATERIALS AND METHODS

Study setting: Department of OBGYN at KLES DR. PRABHAKAR KORE CHARITABLE HOSPITAL AND MEDICAL RESEARCH CENTER, BELAGAVI

Study population: It is a hospital based randomized controlled study conducted on 226 women with prolonged pregnancy, cephalic presentation, with intact membrane and adequate pelvis fitting in inclusion criteria and with no contraindication to vaginal delivery without any fetomaternal high risk factor. Women attending antenatal clinic, who met the inclusion criteria were enrolled in study. Written informed consent taken from patients.

Study period: One year two months (From March 2023 to April 2024)

Study design: randomized controlled trial

Sample size:

$$n = \frac{2 (Z\alpha/2 + Z\beta)^2}{(|\mu_1 - \mu_2| / \sigma)^2}$$
$$d = \frac{|\mu_1 - \mu_2|}{\sigma}$$

Where μ_1 is the mean of the first group, μ_2 is the mean of the second group and σ^2 is the common error variance, for 95% confidence level, Z_{α} value is 1.96 and for 85% power Z_{β} value is 1.036. Difference in change in the bishop score between the two-group assumed as moderate and effect size (d) assumed as 0.4 and from above inputs, sample size required is 113 subjects for each group. Total sample size required is 226 (113×2=226) subjects. Larger the sample better the precision.

Sampling technique: All pregnant women admitted to KLES Dr. Prabhakar B Kore Charitable hospital and medical research center, Belagavi satisfying the inclusion criteria will be included in the study. Written informed consent will be taken from all the participants at the time of admission. Simple random sampling will be used for sampling.

Inclusion Criteria:

1. Women with Ultrasonographically confirmed Singleton pregnancy of 37-42 weeks duration
2. Cephalic presentation
3. No contraindications to vaginal delivery
4. Post dated pregnancies
5. Reactive NST
6. Bishop score \leq 6
7. Either Rh-negative pregnancies/postdatism/oligo/hypertension/macrosomia/mat diabetes/FGR/decreased fetal movements
8. Intact Membranes

Exclusion Criteria:

1. Previous Lower Segment Cesarean Section (LSCS).
2. Placenta Previa/vasa Previa
3. Prior significant uterine or pelvic surgeries
4. Malpresentation.
5. Associated medical disorder
6. (Cardiac disorders, moderate to severe anemia, epilepsy, asthma).
7. Premature Rupture of Membrane (PROM).
8. Mullerian or gross fetal anomalies

9. Hypersensitivity to Prostaglandins & Mifepristone.
10. Active genital herpes
11. Patient not willing to participate
12. Cephalo Pelvic Disproportion.

Methods of data collection:

All subjects fulfilling the inclusion and exclusion criteria were included in the study. Informed consent was taken. Details of the cases were recorded in the prescribed format. History taking and clinical examination was carried out.

Pregnant women of gestational age 37 weeks or more including both registered and unregistered cases at KLE'S Dr. Prabhakar B Kore Charitable Hospital and medical research center, Belagavi will be screened and those who fulfill the inclusion and exclusion criteria will be recruited for the study.

With the approval of the ethical committee written informed consent will be taken from all the participants enrolled for the study. Patients will be classified into 2 groups by computer generated randomized system generated from statistical software R version 4.1.2

The list of randomizations will be concealed and expressed by sequentially numbered sealed envelope just prior to intervention. Each number will allocate the patient to either treatment group A or B.

Group A will receive Tab. Mifepristone 200mg orally on day 1 which is followed by Tab. Misoprostol 25 mcg intravaginally after 24 hrs. and continued 4 hrly till patient goes in active labor with maximum six tablets.

Group B will receive Tab. Misoprostol 25 mcg intravaginally and continued 25 mcg 4 hrly till patient went in active labor with maximum six tablets.

The women will be followed up till they went labour with bishop score >6 and cervical dilatation $>4\text{cm}$.

Successful induction is defined as patient reaching active labor with the dilatation of 4 cm or more (As per ACOG).

Failed induction is defined as failure to reach active labor with the dilatation of 4 cm or more.

Data collection procedure: Patient will be classified into 2 groups by computer generated randomization system generated from statistical software R version 4.1.2. The list of randomizations will be concealed and expressed by sequentially numbered, sealed envelope just prior to intervention. Each number will allocate the patients either to group A or group B.

Data collection tool and Statistical analysis: Data was collected by using a structure proforma. Data entered in MS excel sheet and analysed by using SPSS 24.0 version IBM USA. Qualitative data was expressed in terms of proportions. Quantitative data was expressed in terms of Mean and Standard deviation. Association between two qualitative variables was seen by using Chi square/ Fischer's exact test. Comparison of mean and SD between two groups was done by using unpaired t test to assess whether the mean difference between groups is significant or not. Descriptive statistics of each variable was presented in terms of Mean, standard deviation, standard error of mean.

A p value of <0.05 was considered as statistically significant whereas a p value <0.001 was considered as highly significant.

RESULTS

Out of 4568 deliveries conducted at KLE'S Dr. Prabhakar Kore Charitable hospital and medical research centre for a period of one year two months, 426 participants were screened for the study out of which total 226 participants were recruited after satisfying the inclusion – exclusion criteria and randomized equally into 2 groups of 113-113 each. In the study Group A received Tab. Mifepristone 200mg orally on day 1 which is followed by Tab. Misoprostol 25 mcg intravaginally after 24 hrs and continued 4 hourly till patient goes in active labor with maximum six tablets. Group B received Tab. Misoprostol 25 mcg intravaginally and continued 25 mcg 4 hourly till patient went in active labor with maximum six tablets.

Table 1: Distribution according to age group

		Group A (mife+ miso)		Group B (only miso)		Total	p
		No	%	No	%		
Age group	<20	15	13.3	12	10.6	27	0.81
	21-30	89	78.8	91	80.5	180	
	31-40	9	8.0	10	8.8	19	
Total		113	100.0	113	100.0	226	

Group		N	Mean	Std. Deviation	t	p	Inference
Age	Group A	113	24.66	3.54	-0.56	0.576	Not significant
	Group B	113	24.94	3.81		(>0.05)	

We included total 113 pregnant women in Group A and B. Out of 113 cases from Group A, majority were from 21-30 years age group i.e. 78.8% followed by 13.3% from less than 20 years and 8% from 31-40 years age group. Out of 113 cases from Group B, majority were from 21-30 years age group i.e. 80.5% followed by 10.6% from less than 20 years and 8.8% from 31-40 years age group.

Mean age of the cases from Group A and Group B was 24.66 ± 3.54 and 24.94 ± 3.81 years respectively. We observed no statistically significant difference between two group with respect to age of the mothers ($p > 0.05$).

Figure 1: Bar diagram showing Distribution according to age group

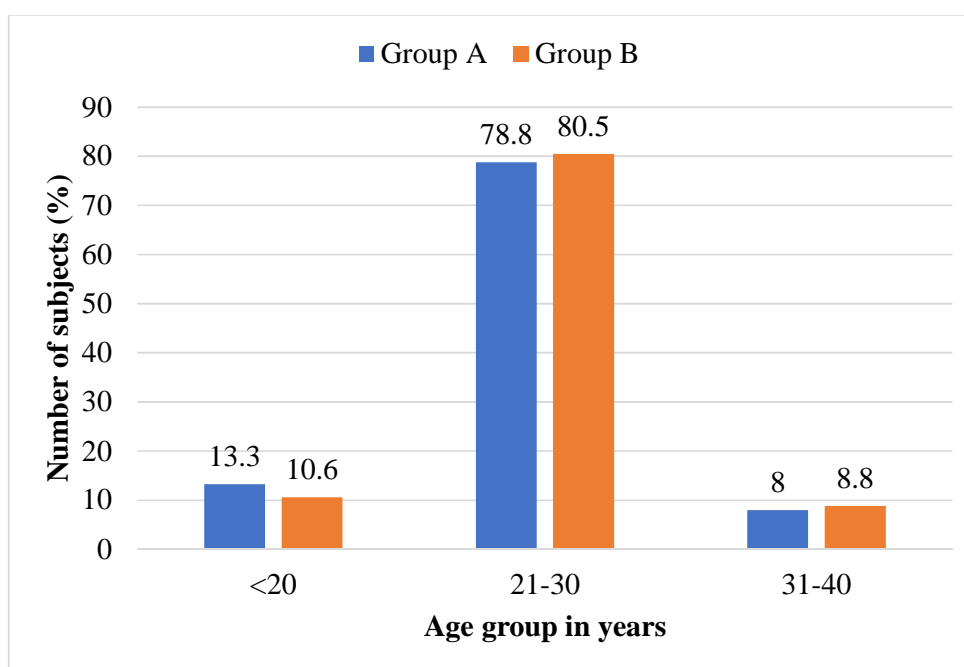


Table 2: Distribution according to gravida status

		Group A (mife+miso)		Group B (only miso)		Total	p
		No	%	No	%		
Gravida status	Primigravida	80	70.8	74	65.5	154	0.39
	Multigravida	33	29.2	39	34.5	72	
Total		113	100.0	113	100.0	226	

70.8% of the pregnant women from Group A were primigravida as compared to 65.5% from Group B. 29.2% of the pregnant women from Group A were multigravida as compared to 34.5% from Group B. This difference in the percentages between two groups was statistically non-significant in our study ($p>0.05$)

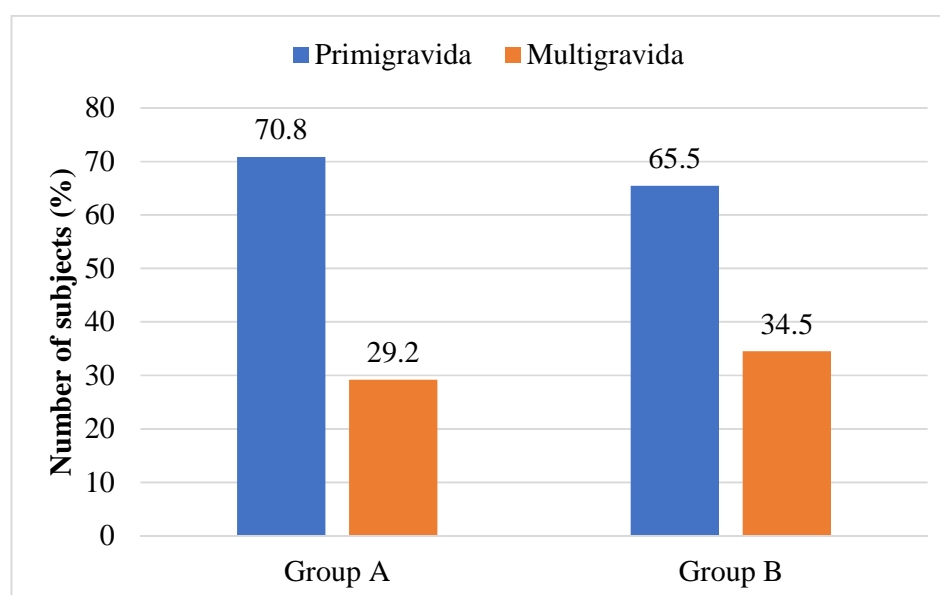
Figure 2: Bar diagram showing Distribution according to gravida status

Table 3 : Comparison of maternal gestational age between Group A and Group B

Group		N	Mean	Std. Deviation	t	p	Inference
Gestational Age at enrolment - weeks	Group A (mife + miso)	113	38.82	1.23	-0.277	0.782	Not significant
	Group B (only miso)	113	38.87	1.17		(>0.05)	

Mean gestational age of the women at enrolment from Group A and Group B was 38.82±1.23 and 38.87±1.17 weeks respectively. We observed no statistically significant difference between two group with respect to gestational age of the mothers (p>0.05).

Figure 3: Bar diagram showing Comparison of maternal gestational age between Group A and Group B

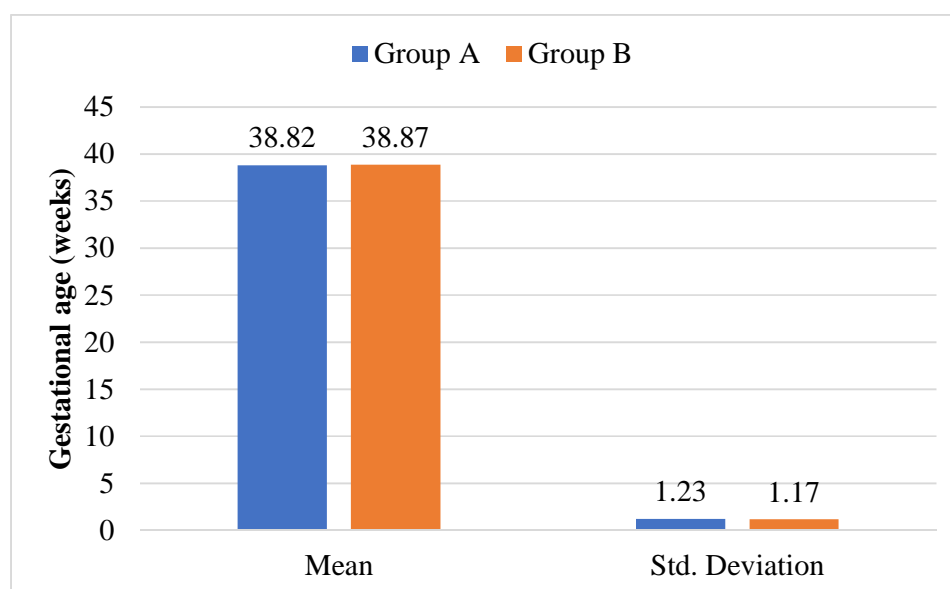


Table 4: Distribution according to BMI

		Group A (mife+miso)		Group B (only miso)		Total	p
		No	%	No	%		
BMI grades	<18.5	3	2.7	4	3.5	7	0.28
	18.5-24.9	101	89.4	94	83.2	195	
	25.0-29.9	9	8.0	12	10.6	21	
	>30.0	0	0.0	3	2.7	3	
Total		113	100.0	113	100.0	226	

Group		N	Mean	Std. Deviation	t	p	Inference
BMI (kg/m ²)	Group A	113	22.46	2.21	-2.067	0.04	Significant
	Group B	113	23.15	2.76		(<0.05)	

8% of the pregnant women from Group A were overweight and obese as compared to 13.3% from Group B. This difference in the percentages between two groups was statistically non-significant in our study ($p>0.05$)

Mean BMI of the women from Group A and Group B was 22.46 ± 2.21 and 23.15 ± 2.76 respectively. We observed statistically significant difference between two group with respect to BMI ($p<0.05$). It means BMI was significantly higher in Group B compared to Group A.

Figure 4: Bar diagram showing Distribution according to BMI

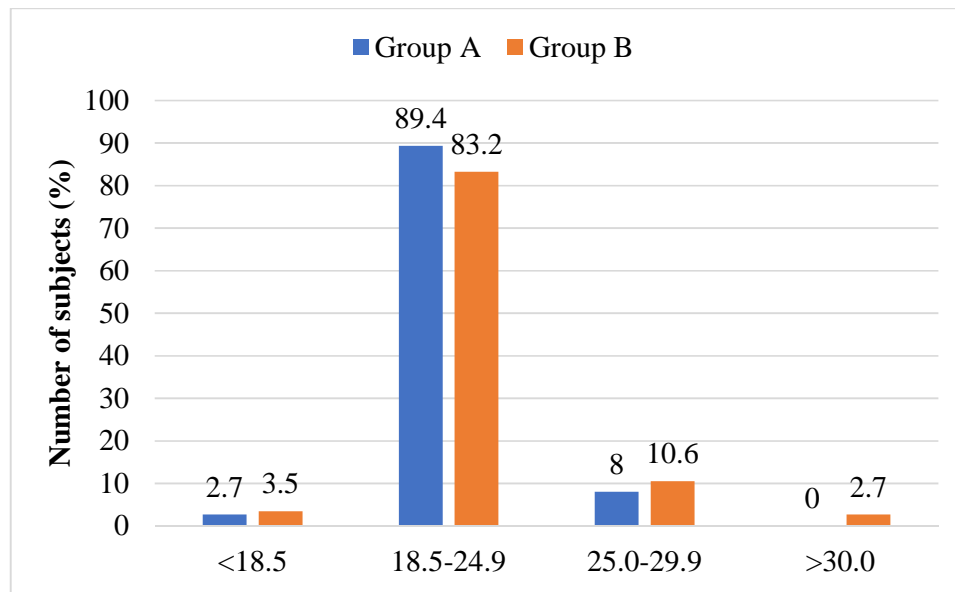


Table 5: Distribution according to various indications for induction of labor

		Group A (mife+miso)		Group B (only miso)		Total	p
		No	%	No	%		
Indications for induction of labor							0.016
	Post datism	39	34.5	41	36.3	80	
	FGR	28	24.8	16	14.2	44	
	Gestational HTN	14	12.4	4	3.5	18	
	Oligamnios	10	8.8	32	28.3	42	
	Rh negative	8	7.1	7	6.2	15	
	Decreased Fetal Movements	6	5.3	5	4.4	11	
	Macrosomia	5	4.4	6	5.3	11	
	GDM	2	1.8	1	0.9	3	
	Overt DM	1	0.9	0	0.0	1	
	Polyhydramnios	0	0.0	1	0.9	1	
		113	100	113	100	226	

Distribution according to risk factors revealed that out of 113 cases from Group A, majority were post-dated pregnancy i.e. 34.5% followed by 24.8 % with fetal growth retardation, 12.4% had gestational hypertension, 8.8% with Oligamnios, 7.1% were Rh negative, 5.3% with delayed fetal movement. Out of 113 cases from Group B, majority were post-dated pregnancy i.e. 36.3% followed by 28.3% with oligohydramnios, 14.2% with fetal growth retardation, 6.2 % were Rh negative and 3.5% had gestational hypertension

Figure 5: Bar diagram showing Distribution according to indications for IOL

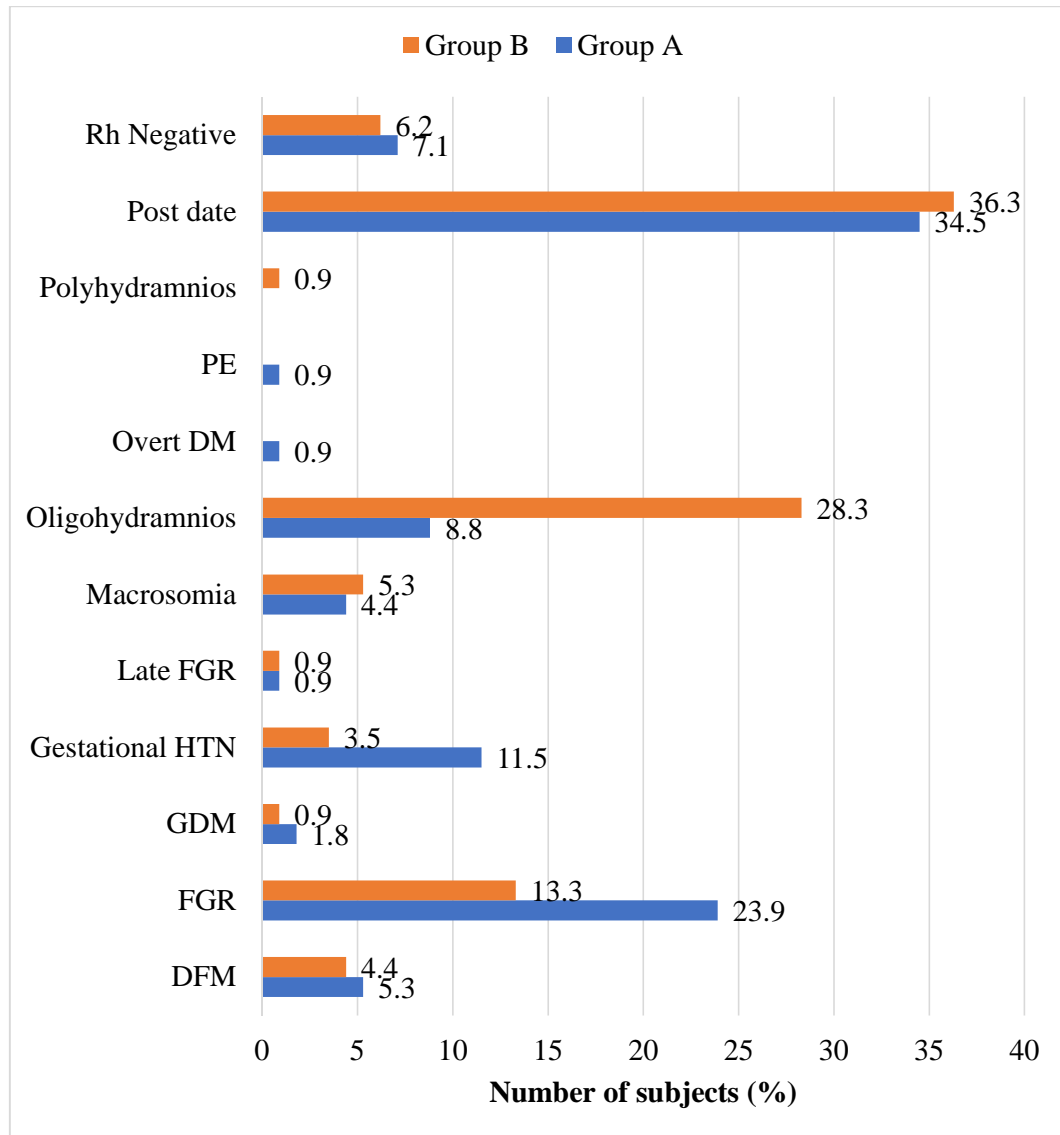


Table 6: Comparison of pre induction Bishops score between Group A and Group B

Group		N	Mean	Std. Deviation	t	p	Inference
Pre induction bishop score	Group A (mife + miso)	113	2.03	2.09	-3.005	0.003	Highly significant
	Group B (only miso)	113	2.85	2.02		(<0.01)	

Mean pre induction Bishops score from Group A and Group B was 2.03 ± 2.09 and 2.85 ± 2.02 weeks respectively. We observed statistically significant difference between two group with respect to pre induction Bishops score ($p < 0.05$). It means pre induction Bishops score was significantly higher in Group B compared to Group A.

Figure 6: Bar diagram showing Comparison of pre induction Bishops score between Group A and Group B

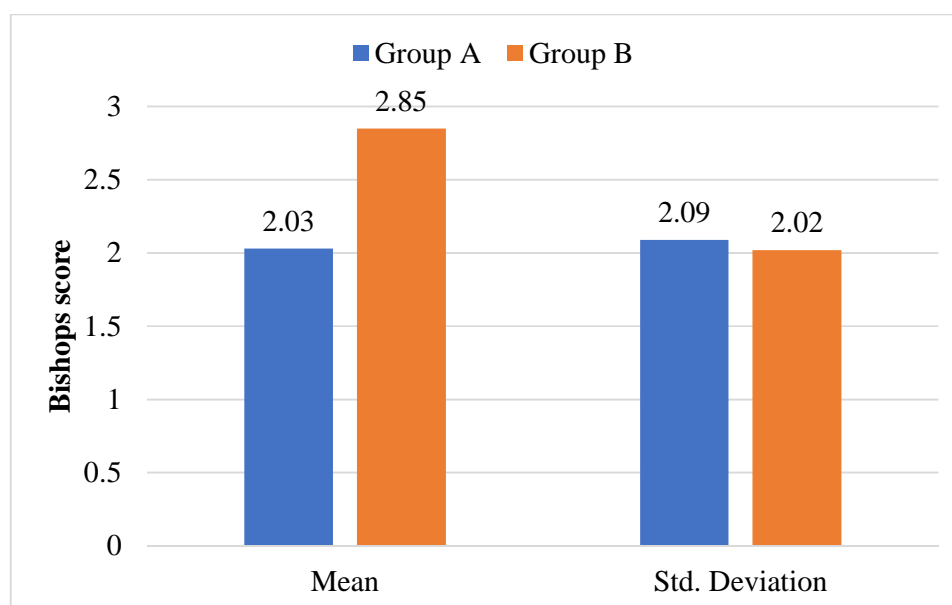


Table 7: Comparison of numbers of misoprostol doses between Group A and Group B

Group		N	Mean	Std. Deviation	t	p	Inference
Total no. of misoprostol used	Group A (mife+miso)	113	2.98	2.13	-2.610	0.009	Highly significant
	Group B (only miso)	113	3.67	1.82		(<0.05)	

Mean numbers of misoprostol in Group A and Group B was 2.98 ± 2.13 and 3.67 ± 1.87 respectively. We observed statistically significant difference between two group with respect to numbers of misoprostol ($p < 0.05$). It means number of doses of misoprostol required in Group B was more as compared to Group A.

Figure 7: Bar diagram showing Comparison of numbers of misoprostol doses between Group A and Group B

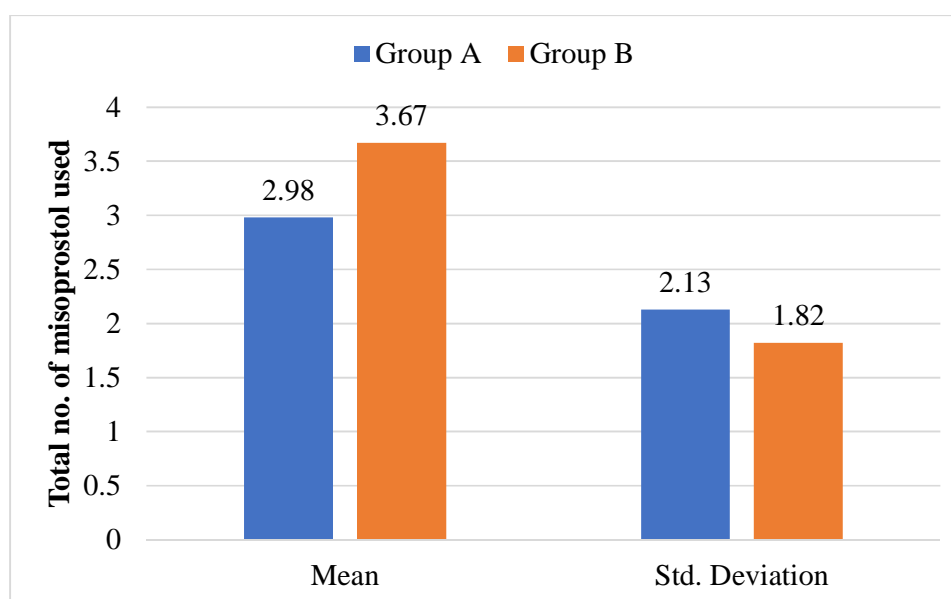


Table 8: Distribution according to number of women that went into active labour

		Group A (mife+miso)		Group B (only miso)		Total	p
		No	%	No	%		
Went into active labour 4 cm	Yes	67	59.3	63	55.8	130	0.26
	No	46	40.7	50	44.2	96	
Total		113	100.0	113	100.0	226	

59.3% of the pregnant women from Group A went into active labour as compared to 55.8% from Group B. This difference in the percentages between two groups was statistically non-significant in our study ($p>0.05$)

Figure 8: Bar diagram showing Distribution according to number of women that went into active labour

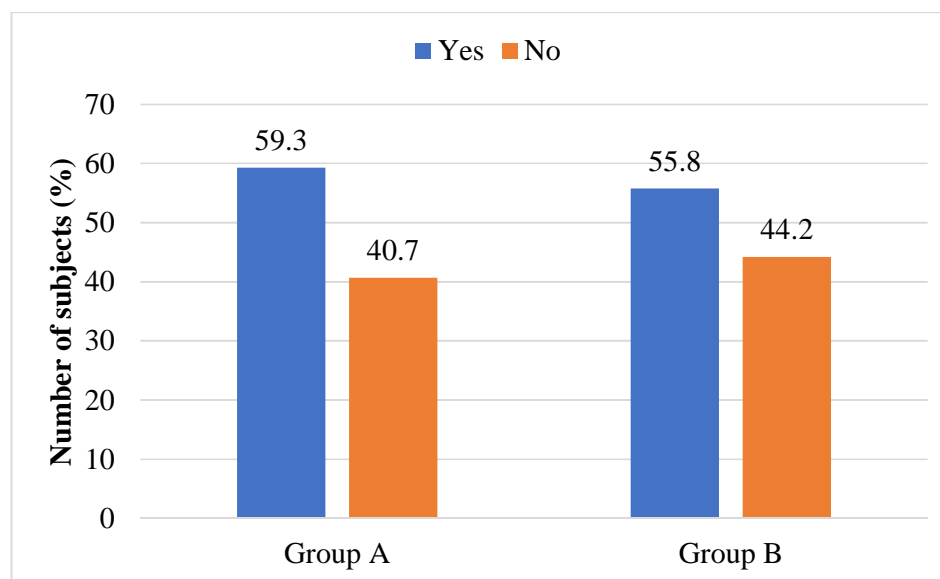


Table 9: Distribution according to maternal complications (if any)

		Group A (mife+ miso)		Group B (only miso)		Total	p
		No	%	No	%		
Maternal complications (if any)	Tachysystole	0	0.0	0	0.0	0	--
	Uterine Hypertonus	0	0.0	0	0.0	0	--

No maternal adverse outcome was observed in either of the group in our study.

Figure 9: Bar diagram showing Distribution according to maternal outcome

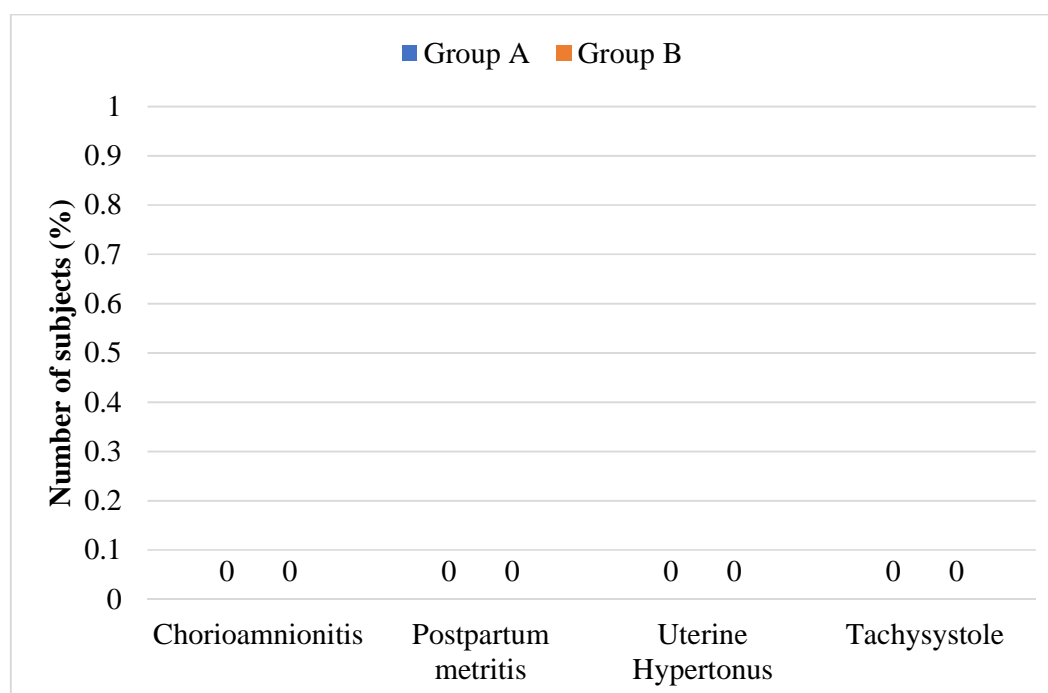


Table 10: Distribution according to mode of delivery

		Group A (mife+miso)		Group B (only miso)		Total	p
		No	%	No	%		
Mode of delivery	Vaginal	58	51.3	51	45.1	109	0.23
	Instrumental	5	4.4	3	2.7	8	
	LSCS	50	44.2	59	52.2	109	
Total		113	100.0	113	100.0	226	

51.3% of the pregnant women from Group A delivered with vaginal delivery as compared to 45.1 % from Group B. 4.4% of the pregnant women from Group A delivered with instrumental delivery as compared to 2.7% from Group B. 44.2% of the pregnant women from Group A underwent LSCS as mode of delivery as compared to 52.2% from Group B. This difference in the percentages between two groups was statistically non-significant in our study ($p>0.05$)

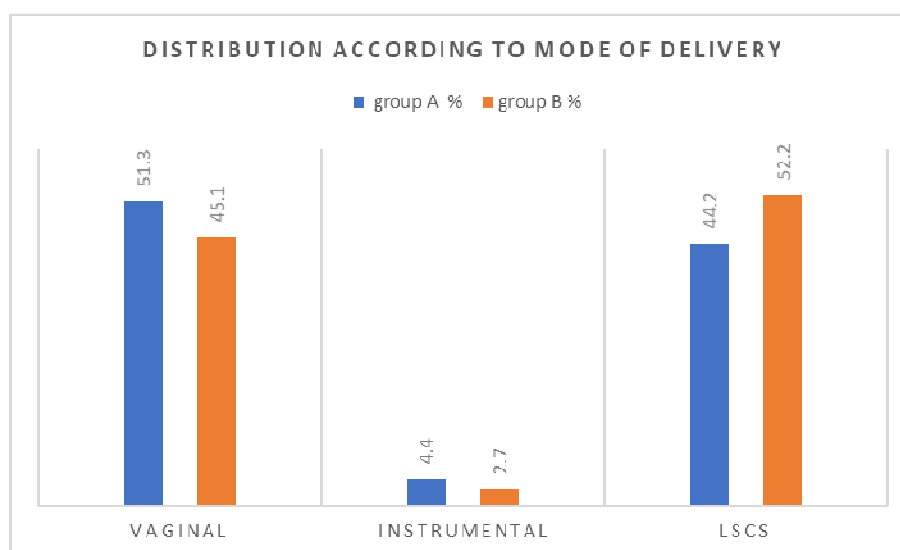
Figure 10: Bar diagram showing Distribution according to mode of delivery

Table 11: Distribution according to delivery only with mifepristone

		Frequency	Percent
Delivered only with mifepristone	Group B (only miso)	112	49.6
	Group A (NO)	98	43.4
	Group A (YES)	16	7.1
	Total	226	100.0

16 women delivered with only mifepristone in Group A i.e. 7.1%.

Figure 11: Bar diagram showing Distribution according to delivery only with mifepristone

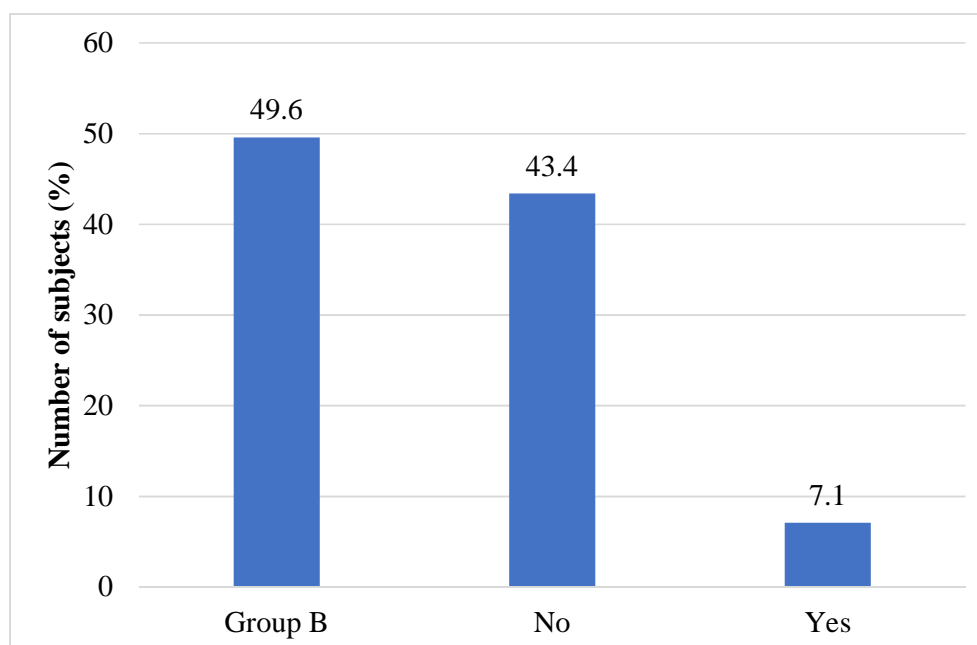


Table 12: Distribution according to indications for LSCS

		Group A (mife+ miso)		Group B (only miso)		Total	p
		No	%	No	%		
Indications for LSCS	Foetal distress	22	19.5	13	11.5	35	0.031
	Failed induction	15	13.3	30	26.5	45	
	2nd stage arrest	0	0.0	2	1.8	2	
	CDMR	1	0.9	0	0.0	1	
	CPD	3	2.7	2	1.8	5	
	MSL	8	7.1	10	8.8	18	
	severe oligo	1	0.9	2	1.8	1	

44.2% of the pregnant women from Group A underwent LSCS as mode of delivery as compared to 52.2% from Group B. In 19.5% women from Group A had fetal distress as indication of LSCS as compared to 11.5% from Group B. 13.3% women from Group A had failed induction as indication of LSCS as compared to 26.5% from Group B. 7.1% women from Group A had meconium-stained liquor as indication of LSCS as compared to 8.8% from Group B. This difference in the percentages between two groups with respect to LSCS indications was found statistically significant in our study ($p < 0.05$).

Figure 12: Bar diagram showing Distribution according to indications for LSCS

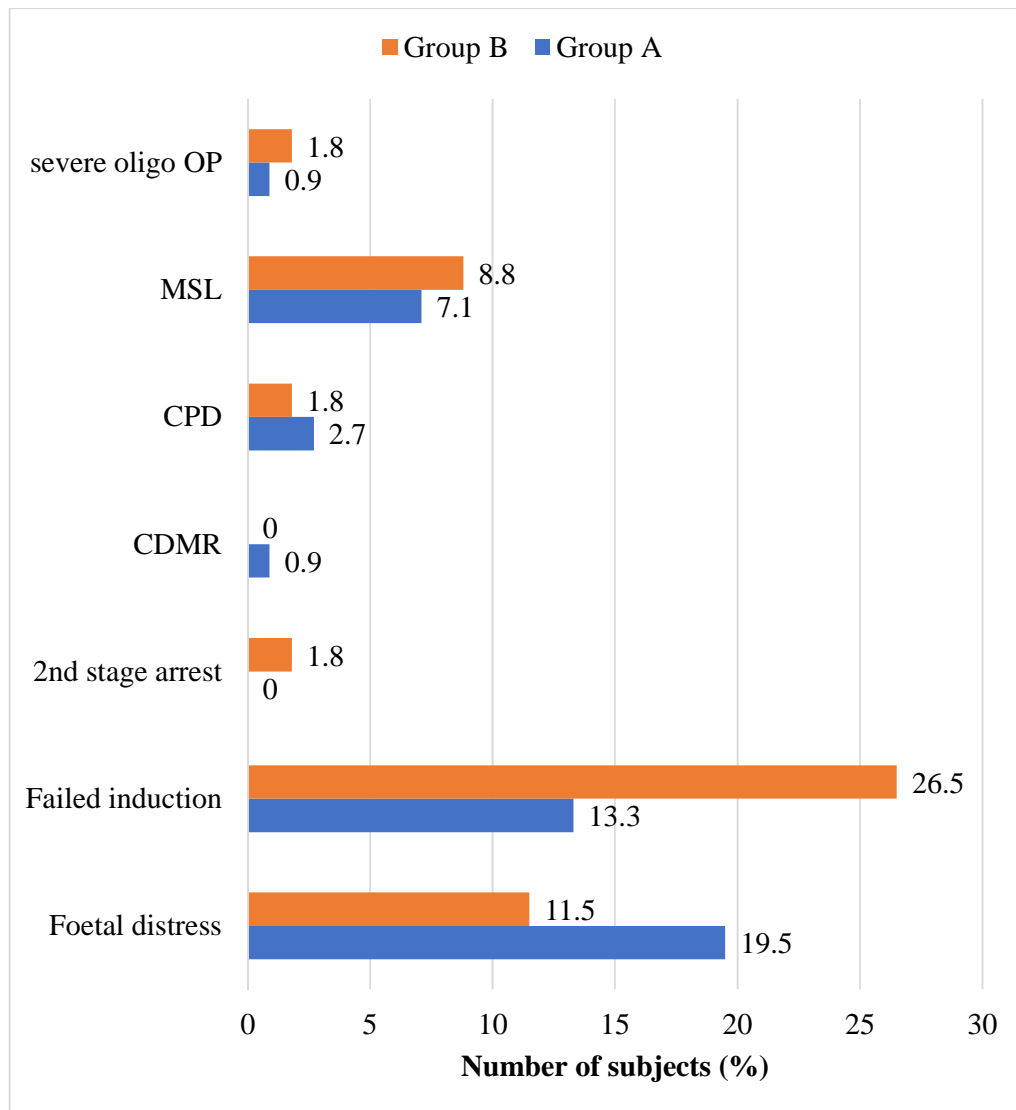


Table 13: Distribution according to mode of delivery in active stage of labour

		Group A (mife+miso)		Group B (only miso)		Total	p
		No	%	No	%		
Mode of delivery in active stage of labour	LSCS	3	4.5	10	15.9	13	0.061
	Vaginal delivery	64	95.5	53	84.1	117	
Total		67	100.0	63	100.0	130	

Mode of delivery in active stage of labour revealed that 4.5% of women from Group A underwent LSCS as compared to 15.9% from Group B. 95.5% of women from Group A underwent normal vaginal delivery as compared to 84.1% from Group B. This difference in the percentages between two groups with respect to indications for NICU admission was statistically non-significant in our study ($p>0.05$).

Figure 13: Bar diagram showing Distribution according to mode of delivery in active stage of labour

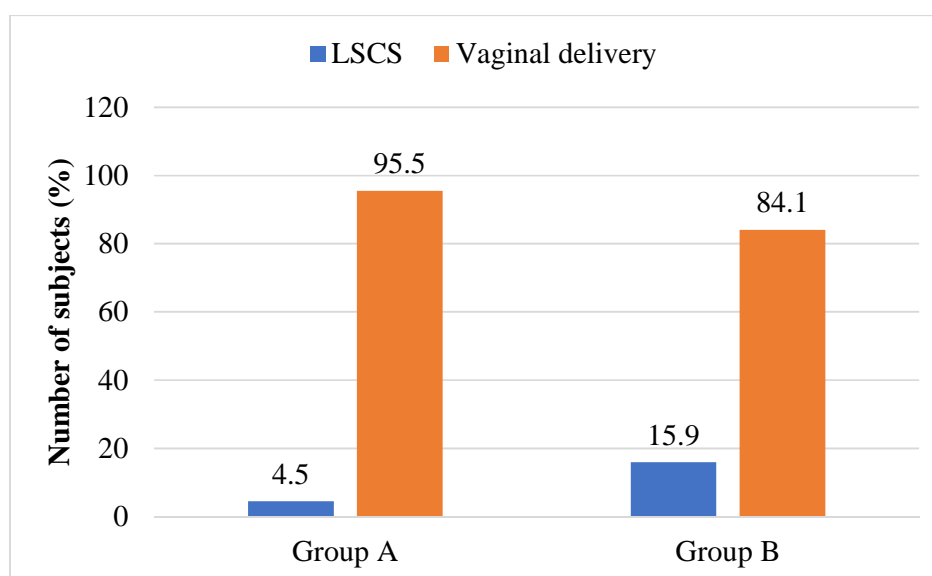


Table 14: Comparison of induction to delivery interval between Group A and Group B

Group		N	Mean	Std. Deviation	t	p	Inference
Induction to delivery interval	Group A (mife+miso)	113	995.06	589.65	-0.960	0.330	Not significant
	Group B (only miso)	113	1139.27	1480.99		(>0.05)	

Mean induction to delivery interval in Group A and Group B was 995.06 ± 589.65 and 1139.27 ± 1480.99 minutes respectively. We observed statistically no significant difference between two group with respect to induction to delivery interval ($p > 0.05$).

Fig 14: Bar diagram showing Induction to delivery interval between both the groups.

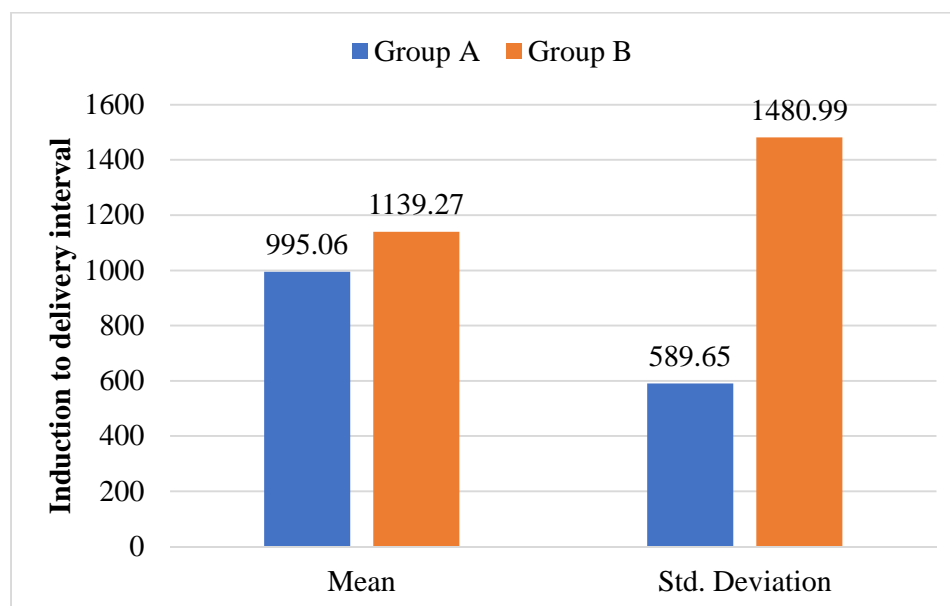


Table 15: Distribution according to neonatal outcome

		Group A (mife+ miso)		Group B (only miso)		Total	p
		No	%	No	%		
Neonatal outcome	Live birth	113	100.0	113	100.0	226	--
	Still birth	0	0.0	0	0.0	0	
Total		113	100.0	113	100.0	226	

We observed no single new-born had still birth in either of the group in our study.

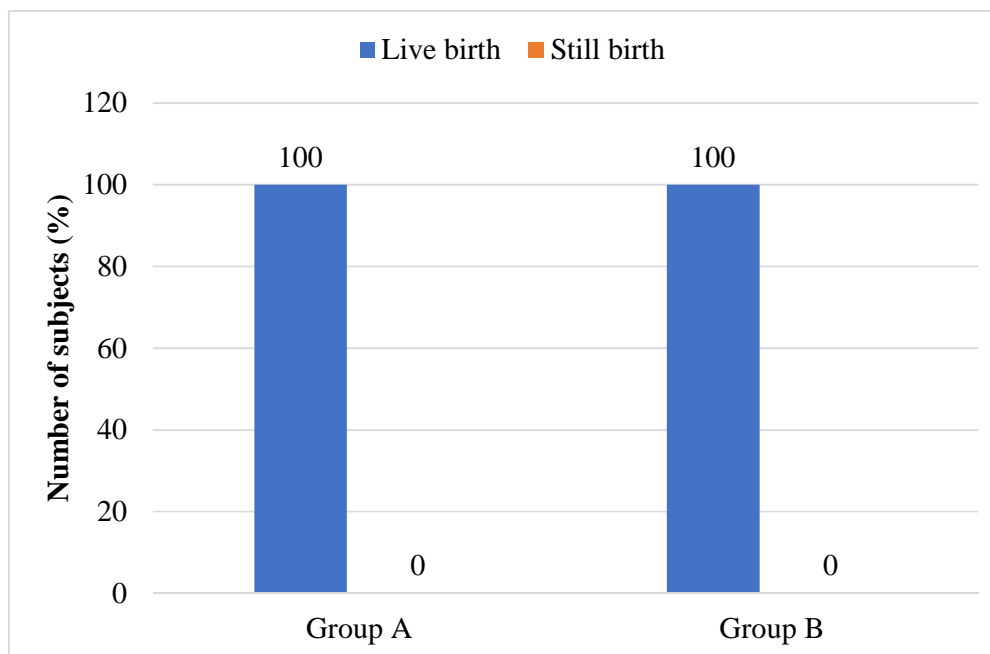
Figure 15: Bar diagram showing Distribution according to neonatal outcome

Table 16: Comparison of APGAR score at 1 minute between Group A and Group B

Group		N	Mean	Std. Deviation	t	p	Inference
Apgar 1 min	Group A (mife+miso)	113	7.02	0.46	-0.557	0.578	Not significant
	Group B (only miso)	113	7.04	0.21		(>0.05)	

Mean APGAR score at 1 minute from Group A and Group B was 7.02 ± 0.46 and 7.04 ± 0.21 respectively. We observed statistically no significant difference between two group with respect to APGAR score at 1 minute ($p > 0.05$).

Figure 16: Bar diagram showing Comparison of APGAR score at 1 minute between Group A and Group B

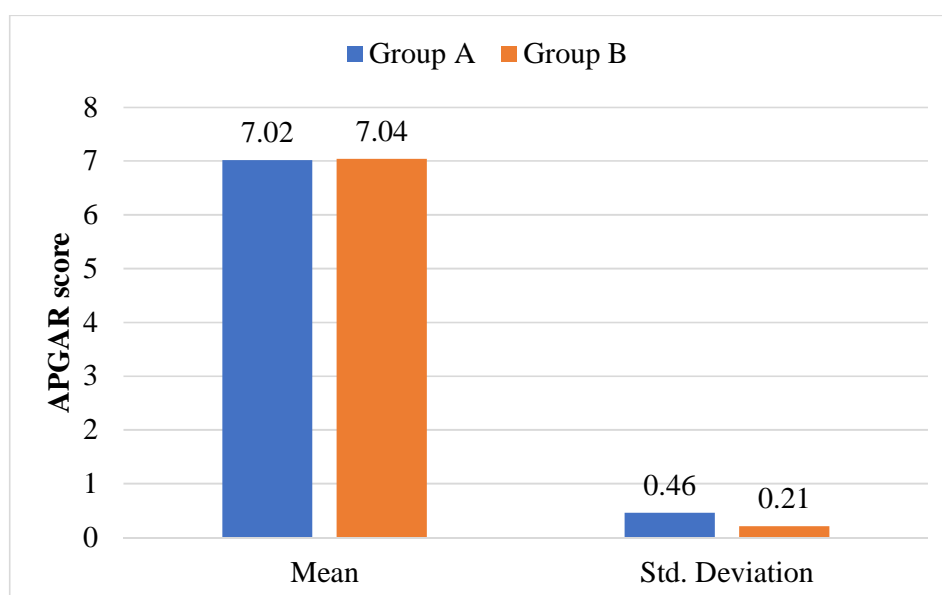


Table 17: Comparison of APGAR score at 5 minute between Group A and Group B

Group		N	Mean	Std. Deviation	t	p	Inference
Apgar 5 min	Group A (mife + miso)	113	8.09	0.59	-1.708	0.089	Not significant
	Group B (only miso)	113	8.2	0.4		(>0.05)	

Mean APGAR score at 5 minutes from Group A and Group B was 8.09 ± 0.59 and 8.2 ± 0.4 respectively. We observed statistically no significant difference between two group with respect to APGAR score at 5 minutes ($p > 0.05$).

Figure 17: Bar diagram showing Comparison of APGAR score at 5 minute between Group A and Group B

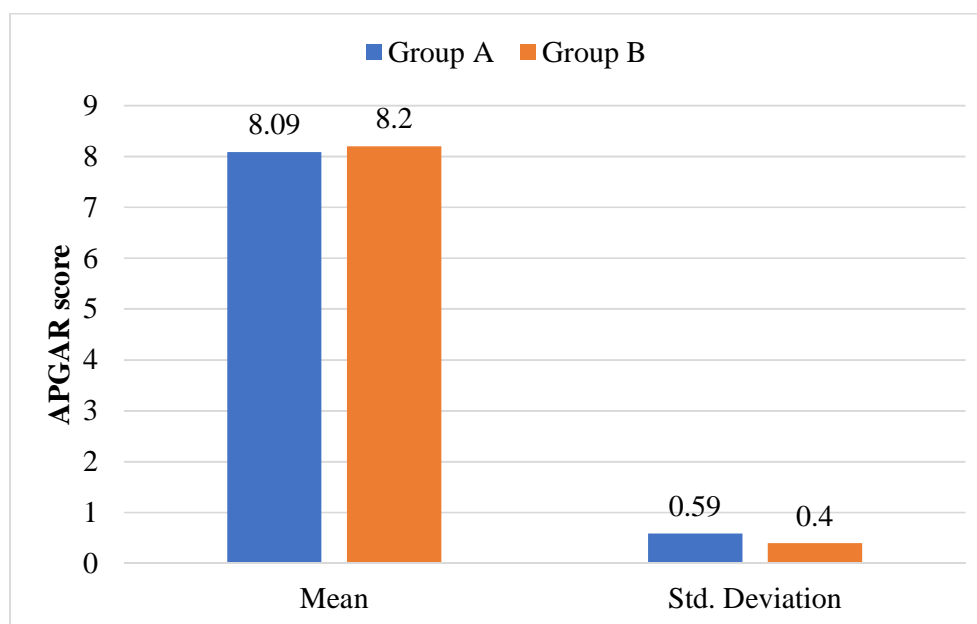


Table 18: Comparison of birth weight between Group A and Group B

Group		N	Mean	Std. Deviation	t	p	Inference
Weight of the baby(kg)	Group A (mife+miso)	113	2.77	0.38	-2.258	0.025	Significant
	Group B (only miso)	113	2.89	0.41		(<0.05)	

Mean birth weight from Group A and Group B was 2.77 ± 0.38 and 2.89 ± 0.41 respectively. We observed statistically significant difference between two group with birth weight ($p < 0.05$). It means birth weight was significantly higher in Group B compared to Group A.

Figure 18: Bar diagram showing Comparison of birth weight between Group A and Group B

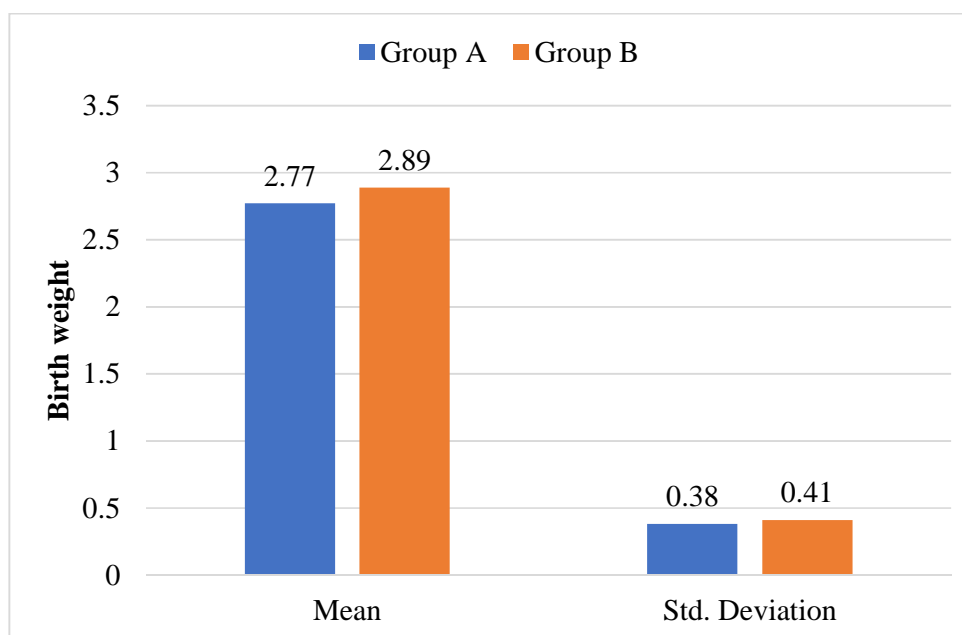


Table 19: Distribution according to gender of the baby

		Group A (mife + miso)		Group B (only miso)		Total	p
		No	%	No	%		
Sex of the baby	Female	55	48.7	62	54.9	117	0.35
	Male	58	51.3	51	45.1	109	
Total		113	100.0	113	100.0	226	

48.7% of the new-borns from Group A were female babies as compared to 54.9% from Group B. 51.3% of the new-borns from Group A were male babies as compared to 45.1% from Group B.

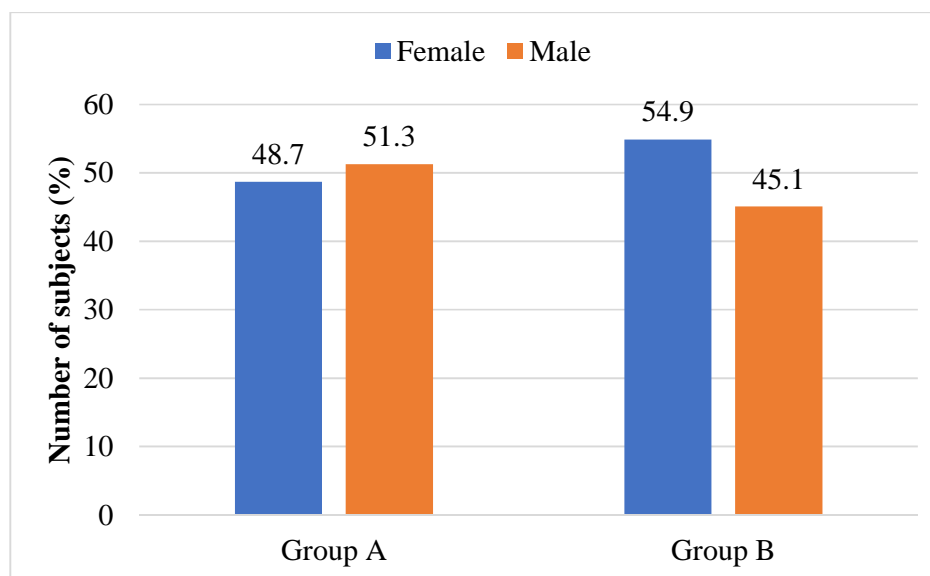
Figure 19: Bar diagram showing Distribution according to gender of the baby

Table 20: Distribution according to NICU admission rate

		Group A (mife +miso)		Group B (only miso)		Total	p
		No	%	No	%		
NICU admission	Yes	32	28.3	23	20.4	55	0.16
	No	81	71.7	90	79.6	171	
Total		113	100.0	113	100.0	226	

NICU admission rate in Group A was 28.3% as compared to 20.4% from Group B. This difference in the percentages between two groups with respect to NICU admission rate was statistically non-significant in our study ($p>0.05$).

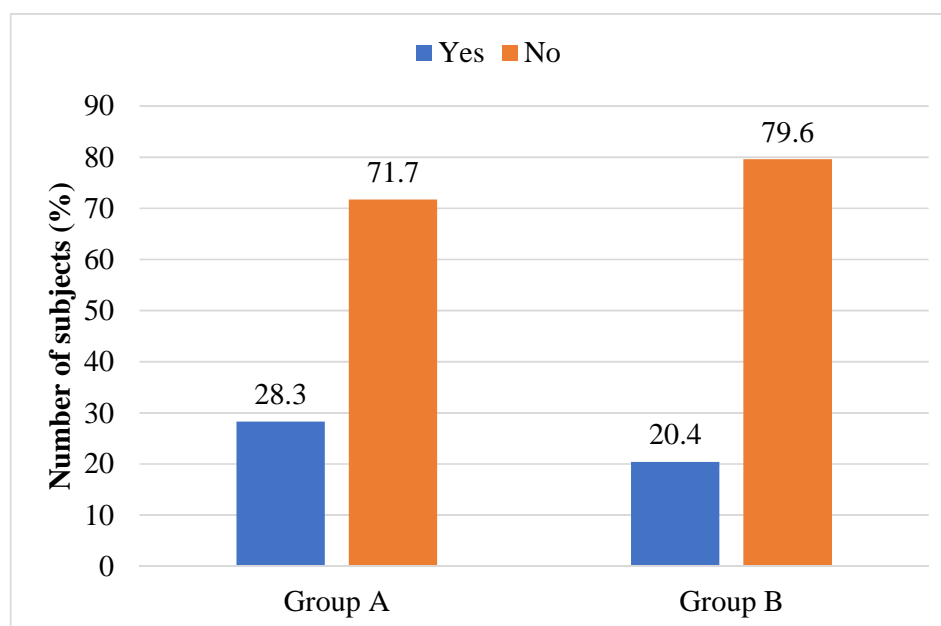
Figure 20: Bar diagram showing Distribution according to NICU admission rate

Table 21: Distribution according to indications for NICU admission

		Group A (mife+ miso)		Group B (only miso)		Total	p
		No	%	No	%		
Reason	Not admitted	81	71.7	90	79.6	171	0.47
	Hyperbilirubinemia	21	18.6	17	15.0	38	
	Hypoglycaemia	2	1.8	1	0.9	3	
	Renal pelviectasis	0	0.0	1	0.9	1	
	Respiratory distress	8	7.1	4	3.5	12	
	Severe respiratory distress	1	0.9	0	0.0	1	
		113	100.0	113	100.0	226	

Distribution according to indications for NICU admission revealed that 18.6% of newborns from Group A had hyperbilirubinemia as compared to 15% from Group B. 7.1% newborns from Group A had respiratory distress as compared to 3.5 % from Group B. 1.8% newborns from Group A had hypoglycaemia as compared to 0.9% from Group B. This difference in the percentages between two groups with respect to indications for NICU admission was statistically non-significant in our study ($p>0.05$).

Figure 21: Bar diagram showing Distribution according to indications for NICU admission

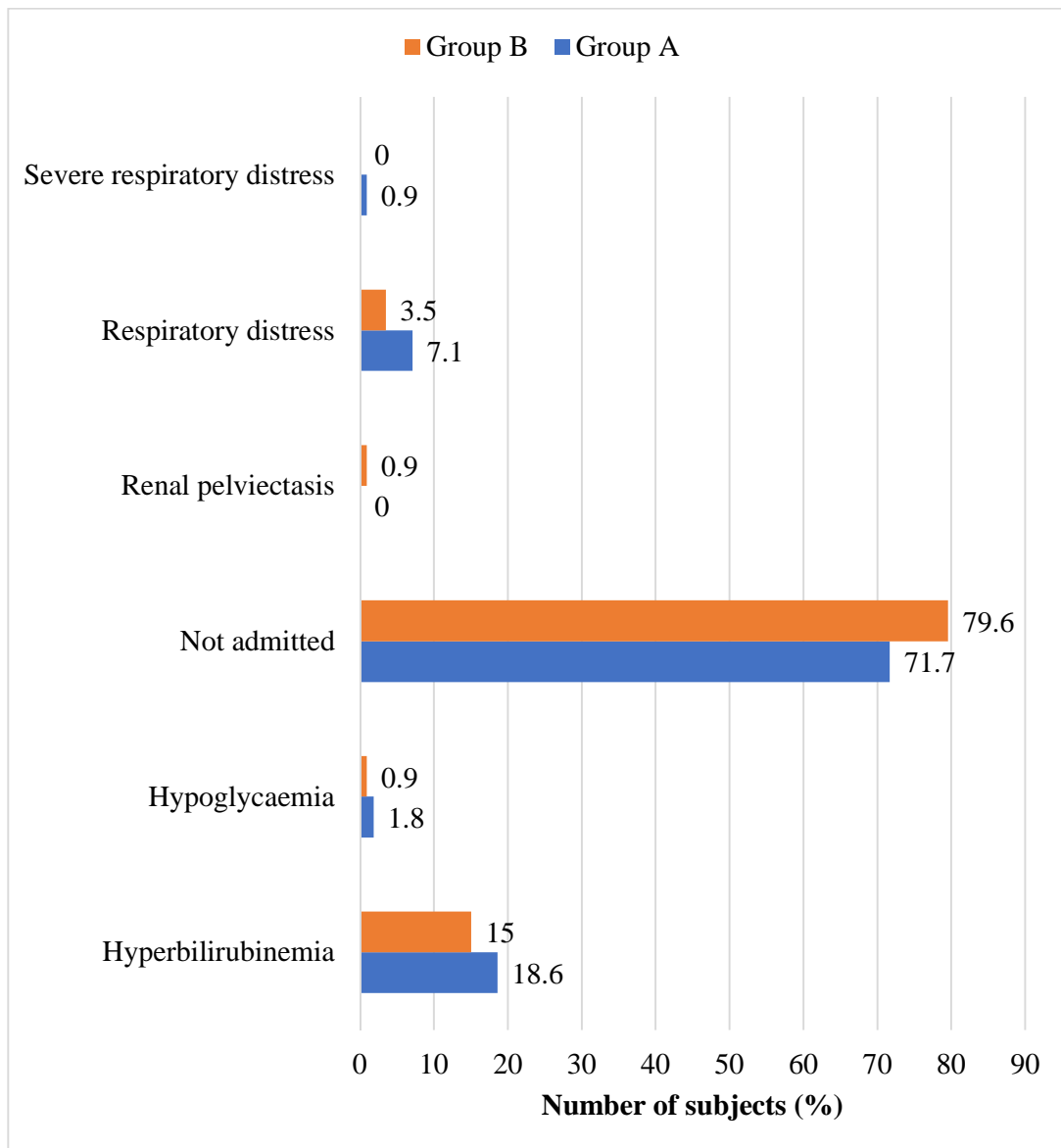
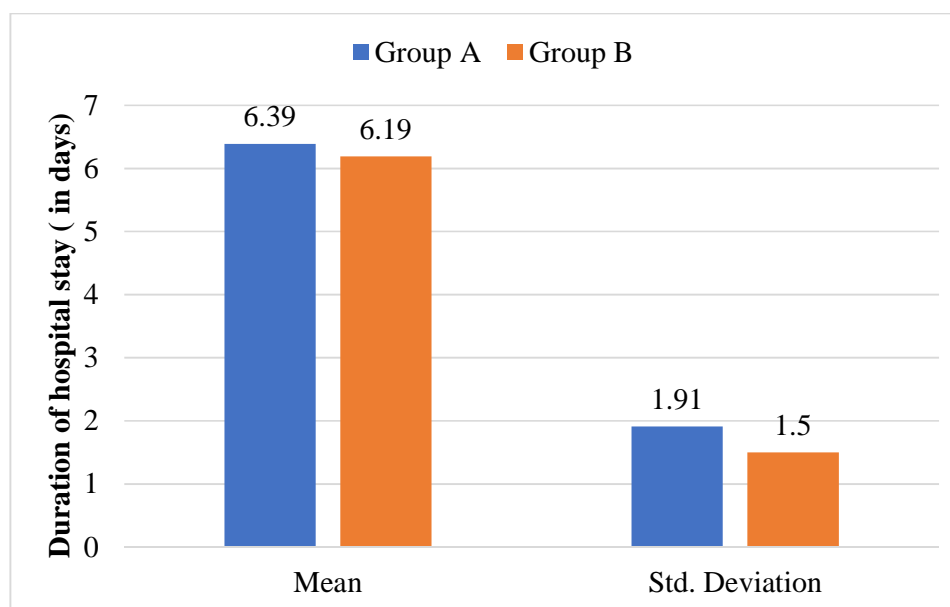


Table 22: Comparison of duration of hospitalisation between Group A and Group B

Group		N	Mean	Std. Deviation	t	p	Inference
Duration of hospital stay (in days)	Group A (mife + miso)	113	6.39	1.91	0.852	0.395	Not significant
	Group B (miso)	113	6.19	1.5		(>0.05)	

Mean duration of hospitalisation from Group A and Group B was 6.39 ± 1.91 and 6.19 ± 1.5 days respectively. We observed statistically no significant difference between two group with respect to duration of hospitalisation ($p > 0.05$).

Figure 22: Bar diagram showing Comparison of duration of hospitalisation between Group A and Group B



DISCUSSION

It is a hospital based randomized controlled study conducted at department of OBGYN at KLES DR. PRABHAKAR KORE CHARITABLE HOSPITAL AND MEDICAL RESEARCH CENTER, BELAGAVI . Out of 4568 deliveries conducted at KLE'S Dr. Prabhakar Kore Charitable hospital and medical research centre for a period of one year two months, 426 participants were screened for the study out of which total 226 participants were recruited after satisfying the inclusion – exclusion criteria and randomized equally into 2 groups of 113-113 each.

Sociodemographic variables of the study groups

We included total 113 pregnant women in Group A and B. Out of 113 cases from Group A, majority were from 21-30 years age group i.e. 78.8% followed by 13.3% from less than 20 years and 8% from 31-40 years age group. Out of 113 cases from Group B, majority were from 21-30 years age group i.e. 80.5% followed by 10.6% from less than 20 years and 8.8% from 31-40 years age group.

In the present study, mean age of the cases from Group A and Group B was 24.66 ± 3.54 and 24.94 ± 3.81 years respectively. We observed no statistically significant difference between two group with respect to age of the mothers ($p>0.05$).

Elliott CL et al⁵⁹ studied to compare the effects of 50 mg or 200 mg of oral mifepristone with placebo on cervical ripening and induction of labour in primigravid women at term with unfavourable cervixes They reported the mean of women in placebo group, mifepristone 50 mg and mifepristone 100 mg group as 26.2 ± 5.9 , 25.8 ± 4.5 and 25.6 ± 3.3 years respectively with no significant difference between the three groups.

Giocalone PL et al⁵² reported that there were no statistical differences (mean \pm 6 standard deviation [SD]) between the mifepristone and placebo groups with regard to maternal age (28.5 ± 4.3 and 28.3 ± 5.0 years, respectively).

McGill J et al⁵⁴ conducted the study and reported the mean age of patients in mifepristone group as 29 ± 5.4 years whereas mean age of patients in Mifepristone/misoprostol group as 30.1 ± 6.9 years.

Yelikar K et al⁵⁶ used Tab. Mifepristone 200 mg orally were assigned in Study Group (n = 50) and who received placebo orally were assigned in Control Group (n = 50). Mean age of the study group 22.98 ± 3.006 years and that of control group was 23 ± 2.893 years.

Sharma R et al⁵⁷ conducted the study by randomising the cases in group A and in group B of 55 patients in each group. Group A received tab Mifepristone+ Misoprostol and group B patients received tablet Misoprostol. 58.2% of the women from group A and 41.8% from group B were from 21-25 years age group. 25.5% of the women from group A and 27.3% from group B were from 31-35 years age group. 7.3% of the women from group A and 21.8% from group B were from below 20 years age group.

Sharma R et al⁵⁷ also reported that mean age of the cases from Group A and Group B was 24.6 ± 3.8 and 24.7 ± 4.6 years respectively. They observed no statistically significant difference between two group with respect to age of the mothers ($p > 0.05$). These findings are consistent with the present study findings.

Gestational age

Mean gestational age of the women at enrolment from Group A and Group B was 38.82 ± 1.23 and 38.87 ± 1.17 weeks respectively. We observed no statistically significant difference between two group with respect to gestational age of the mothers ($p > 0.05$).

Berkane N et al⁵³ reported in their study that gestational age at treatment initiation was 277.2 ± 9.8 days, with no significant difference across the groups. These findings are consistent with our study findings.

Ashtekar Archana et al⁵⁵ reported in their study that mean gestational age of the women at enrolment from Group A and Group B was 37.12 ± 1.3 and 37.8 ± 1.14 weeks respectively. They observed no statistically significant difference between two group with respect to gestational age of the mothers ($p > 0.05$). These findings are consistent with the present study findings.

Obstetrics score

In the present study, 70.8% of the pregnant women from Group A were primigravida as compared to 65.5% from Group B. 29.2% of the pregnant women from Group A were multigravida as compared to 34.5% from Group B. This difference in the percentages between two groups was statistically non-significant in the present study ($p > 0.05$)

In the present study, 83.2% of the pregnant women from Group A were nullipara as compared to 71.7% from Group B. 10.6% of the pregnant women from Group A were primipara as compared to 18.6% from Group B. 6.2% of the pregnant women from Group A were multipara as compared to 9.7% from Group B. This

difference in the percentages between two groups was statistically non-significant in the present study ($p>0.05$)

In the present study, 15.9% of the pregnant women from Group A had past history of abortion as compared to 14.2% from Group B. This difference in the percentages between two groups was statistically non-significant in the present study ($p>0.05$)

In the present study, 15.9% of the pregnant women from Group A had living children as compared to 28.3% from Group B. This difference in the percentages between two groups was statistically significant in the present study ($p<0.05$)

Berkane N et al⁵⁴ reported that two hundred one patients (58.1%) were nulliparous, 88 (25.4%) had been delivered once, and 57 (16.5%) had been delivered more than once.

McGill J et al⁵⁴ conducted the study and reported that 72% from mifepristone group and 72% from Mifepristone/misoprostol group were primigravida.

Risk factors

Distribution according to risk factors revealed that out of 113 cases from Group A, majority were post-dated pregnancy i.e. 34.5% followed by 23.9% with fetal growth retardation, 11.5% had gestational hypertension, 8.8% with oligohydramnios, 7.1% were Rh negative, 5.3% with delayed fetal movement. Out of 113 cases from Group B, majority were post-dated pregnancy i.e. 36.3% followed by 28.3% with oligohydramnios, 13.3% with fetal growth retardation, 6.2 % were Rh negative and 3.5% had gestational hypertension.

Berkane N et al⁵³ in their study reported the risk factors as post term in 31.5% cases (n = 109), hypertension in 29.8% (n = 103), fetal disease (small for gestational age or macrosomia) in 26.9% (n = 93), premature rupture of membranes in 8.7% (n = 30), and polyhydramnios or oligohydramnios in 8.4% (n = 29). Other indications were recorded in 103 cases (29.8%).

Mode of delivery

In the present study, 55.8% of the pregnant women from Group A delivered with normal vaginal delivery as compared to 47.8% from Group B. 44.2% of the pregnant women from Group A underwent LSCS as mode of delivery as compared to 52.2% from Group B. This difference in the percentages between two groups was statistically non-significant in the present study ($p>0.05$)

In the present study, 51.3% of the pregnant women from Group A delivered with spontaneous normal vaginal delivery as compared to 45.1% from Group B. 4.4% of the pregnant women from Group A delivered with instrumental delivery as compared to 2.7% from Group B. This difference in the percentages between two groups was statistically non-significant in the present study ($p>0.05$)

In the present study, 44.2% of the pregnant women from Group A underwent LSCS as mode of delivery as compared to 52.2% from Group B. In 19.5% women from Group A had fetal distress as indication of LSCS as compared to 11.5% from Group B. 13.3% women from Group A had failed induction as indication of LSCS as compared to 26.5% from Group B. 7.1% women from Group A had meconium-stained liquor as indication of LSCS as compared to 8.8% from Group B. This difference in the percentages between two groups with respect to LSCS indications was found statistically significant in the present study ($p<0.05$).

In the present study, mode of delivery in active stage of labour revealed that 4.5% of women from Group A underwent LSCS as compared to 15.9% from Group B. 95.5% of women from Group A underwent normal vaginal delivery as compared to 84.1% from Group B. This difference in the percentages between two groups with respect to indications for NICU admission was statistically non-significant in the present study ($p>0.05$).

Giacalone PL et al⁵² reported that 61% women from mifepristone group and 71.4% from placebo group underwent normal vaginal delivery. 17% women from mifepristone group and 14.3% from placebo group underwent LSCS. 22% women from mifepristone group and 14.3% from placebo group underwent instrumental vaginal delivery.

Elliott CL et al⁵⁹ in their study observed that cervical ripening was successful for 64%, 48%, and 30% of the patients treated with 200 mg, 50 mg of mifepristone, and placebo, respectively. This difference was statistically significant for the 200 mg group ($P = .01$, odds ratio (OR) 4.15, 95% confidence interval (CI) 1.34, 12.84). There was no statistically significant difference between the 50-mg mifepristone group and the placebo group ($P = .18$, OR 2.36 95% CI 0.66, 8.37). The number of patients in spontaneous labour after 72 hours was 9 (36%), 8 (32%), and 7 (23.33%) in the 200-mg, 50-mg and placebo groups, respectively.

Giacalone PL et al⁵² conducted the study with the objective to determine the efficacy and safety of mifepristone for cervical ripening in post-term pregnancies. 68.3% women from mifepristone group and 33.3% from placebo group went into spontaneous labour with statistically significant difference between two groups showing effect of mifepristone ($P<0.05$).

McGill J et al⁵⁴ conducted the study and reported that 51.5% women from mifepristone only group and 11.8% from mifepristone and misoprostol group underwent spontaneous vaginal delivery. 24.2% women from mifepristone only group and 64.7% from mifepristone and misoprostol group underwent LSCS delivery.

Sharma R et al⁵⁷ reported that 81.8% of patients delivered vaginally and 18.2% undergone caesarean section in Group A while 72.7% delivered vaginally and 23.6% undergo caesarean section in Group B.

Ashtekar Archana et al⁵⁵ reported in their study that In Group A, 16 patients delivered by only T. Mifepristone out of which 11 are delivered vaginally and 5 by emergency caesarean section. In Group A, total 20 patients i.e.40% are delivered by caesarean section and 29 i.e. 58% are delivered vaginally and 1 patient required instrumental (forceps) delivery. In Group B, 5 patients i.e. 10 % required caesarean section and 42 (84%) delivered spontaneously vaginally and 3 patients required instrumental (2 forceps and 1 vacuum) delivery. So, incidence of caesarean section is found more in Group A than Group B which is significant.

Yelikar K. et al⁵⁶ in their study observed that Six women (12 %) in Study Group and eight women (16 %) in Control Group underwent caesarean section. 4% in Study Group and 10% in Control Group underwent instrumental delivery.

Active labour progress

In the present study, 59.3% of the pregnant women from Group A went into active labour as compared to 55.8% from Group B. This difference in the percentages between two groups was statistically non-significant in the present study ($p>0.05$)

McGill J et al⁵⁴ conducted the study and reported that 51.5% women from mifepristone only group and 11.8% from mifepristone and misoprostol group underwent spontaneous vaginal delivery. 24.2% women from mifepristone only group and 64.7% from mifepristone and misoprostol group underwent LSCS delivery.

In a retrospective study, Gallot and colleagues⁶⁰ categorized 89 women whose labor was induced with 200 mg of mifepristone into those who had onset of labor within 48 h of mifepristone administration (51 women) and those who did not. Most of the latter received PGE₂ vaginally, and the results suggest that there were significantly more caesarean sections among them — especially when high doses of prostaglandins were used. The findings from the present study are in agreement with these results.

In 3 previous studies^{59,52,61} mifepristone has been shown to be effective in initiating spontaneous labour or successfully ripening the cervix in 64%, 77%, and 80.5% of women, respectively, compared with placebo. The dose of mifepristone used varied from 50 mg, to 2 doses of 200 mg every 24 h, to 600 mg. While 600 mg was associated with more hyperstimulation when prostaglandins or oxytocin were used in conjunction⁶¹, 50 mg was found not to be as effective as 200 mg. In this study, a dose of 400 mg was used. Two reported trials have used a combination of vaginal misoprostol with mifepristone.^{62,63}

In the study by Wing and coworkers⁶³, 25 µg of misoprostol was administered vaginally 24 h after administration of 200 mg of mifepristone or placebo. While results showed a modest increase in the number of women who were delivered vaginally within 48 h of induction (87.5% of women treated with mifepristone and 70.8% of women who received placebo [P= 0.01]), the authors speculated that longer

exposure to mifepristone might be required to show significant clinical differences in labour induction.

Maternal outcome

No maternal adverse outcome was observed in either of the group in the present study.

Berkane N et al⁵³ in their study reported the maternal outcome in terms of four serious maternal AEs occurred, comprising 3 cases of uterine Hypertonus (2 in the 50 mg group, 1 in the 400 mg group) and 1 case of maternal bradycardia (in the 600 mg group).

Fetal outcome

Mortality as fetal outcome

We observed no single newborn or still birth in either of the group in the present study.

NICU admission as fetal outcome

NICU admission rate in Group A was 28.3% as compared to 20.4% from Group B. This difference in the percentages between two groups with respect to NICU admission rate was statistically non-significant in the present study ($p>0.05$).

Distribution according to indications for NICU admission revealed that 18.6% of newborns from Group A had hyperbilirubinemia as compared to 15% from Group B. 7.1% newborns from Group A had respiratory distress as compared to 3.5 % from Group B. 1.8% newborns from Group A had hypoglycaemia as compared to 0.9% from Group B. This difference in the percentages between two groups with respect to

indications for NICU admission was statistically non-significant in the present study ($p>0.05$).

Elliott CL et al⁵⁹ in their study observed that neonatal jaundice was reported in seven (28%), two (8%), and two (6.7%) of the infants of mothers who received 200 mg of mifepristone, 50 mg of mifepristone, and placebo, respectively. All of these cases resolved spontaneously and were not considered clinically significant.

Berkane N et al⁵³ in their study reported the fetal outcome in terms of NICU admission for the indications like hypoglycaemia in 26% newborns in placebo group vs 32% in mifepristone group. 7% newborns in placebo group experienced jaundice vs 10% in mifepristone group. 2% newborns in placebo group experienced jaundice vs 3% in mifepristone group.

Ashtekar Archana et al⁵⁵ reported in their study that the fetal distress was present in 19 (38%) cases in Group A with T. Mifepristone with T. Misoprostol while it was present in only 9(18%) cases in Group B with T. Misoprostol which is statistically found to be significant. These findings are not consistent with the present study findings.

Yelikar K. et al⁵⁶ in their study observed that perinatal outcome was assessed and comparison was made between healthy baby and Babies with adverse outcome (perinatal death/NICU admission) in the Study Group and Control Group, it was not found to be significant. In Study Group, out of four babies who were admitted to NICU for Apgar\7 at 5 min, three babies survived and one baby died on 7th day due to meconium aspiration syndrome. In Control Group, two babies were admitted in NICU for thick meconium and discharged successfully.

Birth weight

Mean birth weight from Group A and Group B was 2.77 ± 0.38 and 2.89 ± 0.41 respectively. We observed statistically significant difference between two group with birth weight ($p<0.05$). It means birth weight was significantly higher in Group B compared to Group A.

Elliott CL et al⁵⁹ reported the mean birth weight from Group A and Group B was 2.8 ± 0.4 and 2.92 ± 0.65 kg respectively. They observed statistically significant difference between two group with birth weight ($p<0.05$). These findings are consistent with the present study findings.

APGAR score and birth asphyxia

Mean APGAR score at 1 minute from Group A and Group B was 7.02 ± 0.46 and 7.04 ± 0.21 respectively. We observed statistically no significant difference between two group with respect to APGAR score at 1 minute ($p>0.05$).

Mean APGAR score at 5 minutes from Group A and Group B was 8.09 ± 0.59 and 8.2 ± 0.4 respectively. We observed statistically no significant difference between two group with respect to APGAR score at 5 minutes ($p>0.05$).

Giocalone PL et al⁵² reported that APGAR score of less than 7 in 7.3% of newborns in mifepristone group as compared to placebo group with 4.3%. They also observed statistically no significant difference between two groups with respect to APGAR score. These findings are consistent with the present study findings.

Ashtekar Archana et al⁵⁵ reported in their study that the incidence of birth asphyxia was similar in both the groups. In Group A only 7 babies and in Group B

only 6 babies had their APGAR score < 8 whereas in rest all babies the APGAR score was good.

Bishops score

Mean pre induction Bishops score from Group A and Group B was 2.03 ± 2.09 and 2.85 ± 2.02 weeks respectively. We observed statistically significant difference between two group with respect to pre induction Bishops score ($p < 0.05$). It means pre induction Bishops score was significantly higher in Group B compared to Group A.

Giacalone PL et al⁵² reported the bishops score as mean value of 6 in mifepristone as compared to placebo group with statistically significant difference between two group ($p < 0.05$) which is compared to the present study findings.

Giacalone PL et al⁵² reported that eighteen of 41 patients in the mifepristone group had an evaluation of the Bishop score on day 2, compared with 29 of 42 patients in the placebo group. Strict success for cervical ripening was achieved for ten mifepristone subjects compared with eight in the placebo group (55.5% versus 27.5%, respectively; $P = .004$). Spontaneous onset of labour on days 1 and 2 was significantly more frequent in patients treated with mifepristone than with placebo. Among the 23 remaining patients from the mifepristone group whose Bishop score on day 2 was not evaluated, seven delivered before day 1, 12 delivered on day 1, and four delivered on day 2 before evaluation of the score.

McGill J et al⁵⁴ conducted the study and reported that mean pre induction Bishops score from group receiving PGE2 and other group with mifepristone/misoprostol was 3.2 ± 1.8 and 3.6 ± 1.8 respectively with no difference between two groups ($p > 0.05$). These findings are not consistent with the present study findings.

Ashtekar Archana et al⁵⁵ reported in their study that mean pre-induction Bishop's score was 4.50 in Group A. It was increased by 6.80 in 6 hrs and 8.22 after 12 hrs. The mean pre induction Bishop's score was 4.72 in Group B. It was increased by 5.94 in 6 hrs and 7.81 after 12 hrs. So it is found that Bishop's score is significantly improved in Group A with T. Mifepristone with T. Misoprostol than only with T. Misoprostol in Group B which was statistically significant. These findings are consistent with the present study findings.

Yelikar K. et al⁵⁶ in their study stated that mean pre induction Bishops score for study group was 2.02 ± 0.749 and for control group was 2.16 ± 0.77 with no difference between two groups. At the end of 24 h, there was a significant improvement in mean Bishop's score in Study Group (5.04082 ± 1.90) compared with Control Group (3.26 ± 1.15) with statistically significant difference between two groups.

Sharma R et al⁵⁷ also reported that 49.1% of the patients were having bishop's score between 0-1 in Group A and 69.1% of the patients in combination group i.e. B were having Bishop's score 0-1 when patients were admitted. Mean Bishop's score observed in Group A were 2.5 ± 1.78 and 1.67 ± 1.25 in Group B. They also reported that there was significant improvement in the Bishop's score after giving Mifepristone to the patients; mean Bishop's 24 hours after mifepristone were 4.03 ± 1.80 . These findings are consistent with the present study findings.

BMI comparison

In our study, 8% of the pregnant women from Group A were overweight and obese as compared to 13.3% from Group B. This difference in the percentages between two groups was statistically non-significant in the present study ($p > 0.05$)

Mean BMI of the women from Group A and Group B was 22.46 ± 2.21 and 23.15 ± 2.76 respectively. We observed statistically significant difference between two group with respect to BMI ($p < 0.05$). It means BMI was significantly higher in Group B compared to Group A.

Yelikar K. et al⁵⁶ in their study stated that mean BMI for study group was 20.08 ± 1.56 and for control group was 21.03 ± 0.86 with no significant difference between two groups. These findings are contrast to the present study findings.

Induction to delivery interval

In the present study, mean induction to delivery interval in Group A and Group B was 995.06 ± 589.65 and 1139.27 ± 1480.99 minutes respectively. We observed statistically no significant difference between two group with respect to induction to delivery interval ($p > 0.05$).

In the present study we found clinically significant improvement (though not statistically significant) in Bishops score in group A (T. Mifepristone with T. Misoprostol) compare with Group B (T. Misoprostol) this suggests that tab. Mifepristone has got dual role as cervical ripening agent and also as labour inducing agent. This drug causes reduction in induction –delivery interval

Giocalone PL et al⁵² reported that onset of labour in the mifepristone group occurred significantly faster (median [range]) than in the placebo group ($31.7 [9.5-117.8]$ versus $53.9 [2.5-192.0]$ hours; $P = 0.02$). They also observed statistically no significant difference between two group with respect to induction to delivery interval ($p > 0.05$) which is consistent with the present study findings.

Ashtekar Archana et al⁵⁵ reported in their study that the mean Induction–delivery interval in Primigravidae in Group A was 10.50 hrs while in Multigravida was 8.68 hrs. While in Primigravidae in Group B was 13.83 hrs and in multigravida was in 9.88 hrs. The Induction Delivery interval in multigravida is less in both the groups than primigravidae.

They also reported that overall mean Induction – delivery interval was 9.59 hrs in Group A and in Group B, it was 11.78 hrs. It means that induction delivery interval duration is less in Group A (T. Mifepristone with T. Misoprostol) than in Group B with T. Misoprostol. These findings are in contrast with the present study findings.

Yelikar K. et al⁵⁶ in their study stated that mean induction to active phase interval was $1,598 \pm 346$ min in Study Group compared with $1,763 \pm 210$ min in Control Group which was found to be statistically significant. These findings are in contrast with the present study findings.

Sharma R et al⁵⁷ reported that mean induction-delivery interval was more in Group A that was 19 ± 12.2 hours as compared to 13.1 ± 13.0 hours in Group B which was found to be statistically significant. These findings are in contrast with the present study findings.

Numbers of misoprostol doses

Mean numbers of misoprostol in Group A and Group B was 2.98 ± 2.13 and 3.67 ± 1.87 respectively. We observed statistically significant difference between two group with respect to numbers of misoprostol ($p < 0.05$). It means number of doses of misoprostol required in Group B was more as compared to Group A.

Yelikar K. et al⁵⁶ in their study observed that mean dose requirement of misoprostol in Study Group was 40 ± 27.2 mcg compared with 52 ± 19.46 mcg in Control Group. This was found to be statistically significant.

Labour with only mifepristone

16 women delivered with only mifepristone in Group A i.e. 7.1%.

Stenlund PM et al⁶⁴ found 79.2% women went in labor without Tab. Misoprostol,

Another study by Su H et al⁶⁵ states that 22.58% women went in labor without Tab. Misoprostol.

J McGill et al⁵⁴ found 66% women went in labor without Tab. Misoprostol.

Elliot CL et al⁵⁹ found in their conclusion that Tab. Mifepristone is known to cause softening and dilatation of cervix and increase in uterine activity.

Lil L et al⁶⁶ found Bishops score was higher in women induced with Tab. Mifepristone.

Strengths of the study

The study's comparative design with randomized groups provide a robust evaluation on the effect of Tab Mifepristone and Misoprostol V/S Misoprostol alone in the induction of labor. Clear inclusion and exclusion criteria, comprehensive data collection and appropriate statistical analysis enhances its validity. Detailed reporting on the side effects and consistency with the previous studies add clinical relevance. The results are reassuring regarding labor and feto-maternal outcomes.

Limitations of the study

The study findings couldn't be generalized because of the small sample size. Furthermore, the research was carried out exclusively at one location, thus restricting the generalizability of the results to alternative contexts with distinct patient demographics and medical procedures. The most appropriate time interval mifepristone and misoprostol administration, its dose and route of administration, cost effectiveness and patient acceptability are questions to be explored.

CONCLUSION

The present randomized controlled trial study was carried out at Department of OBGY at KLES DR. PRABHAKAR KORE CHARITABLE HOSPITAL AND MEDICAL RESEARCH CENTER, BELAGAVI for a period of one year two months from March 2023 to April 2024 with the objective to determine the effect of mifepristone and misoprostol VS misoprostol alone in induction of labor and also to determine the fetomaternal outcome. Out of 4568 deliveries, 426 participants were screened and the study was conducted on 226 women fitting in inclusion criteria and with no contraindication to vaginal delivery without any fetomaternal high-risk factor. The patients were distributed in two groups randomly.

GROUP A PATIENTS: It consists of 113 patients. They received Tab. Mifepristone. 200mg orally on day 1 which is followed by Tab. Misoprostol 25 mcg intravaginally after 24 hours and continued 4 hourly till patient goes in active labor with maximum six tablets.

GROUP B PATIENTS: It consists of 113 patients. They received Tab. Misoprostol 25 mcg intravaginally and continued 25 mcg 4 hourly till patient went in active labor with maximum six tablets. After admission in ward, initial information about the study was given and a written informed consent was taken.

The results of the present study are summarised as follows:

Group A received Tab. Mifepristone 200mg orally on day 1 which is followed by Tab. Misoprostol 25 mcg intravaginally after 24 hrs and continued 4 hrly till patient goes in active labor with maximum six tablets. **Group B** received Tab. Misoprostol 25 mcg intravaginally and continued 25 mcg 4 hrly till patient went in active labor with maximum six tablets.

We included total 113 pregnant women in Group A and B. Out of 113 cases from Group A, majority were from 21-30 years age group i.e. 78.8% followed by 13.3% from less than 20 years and 8% from 31-40 years age group. Out of 113 cases from Group B, majority were from 21-30 years age group i.e. 80.5% followed by 10.6% from less than 20 years and 8.8% from 31-40 years age group.

Distribution according to risk factors revealed that out of 113 cases from Group A, majority were post-dated pregnancy i.e. 34.5% followed by 23.9% with fetal growth retardation, 11.5% had gestational hypertension, 8.8% with oligohydramnios, 7.1% were Rh negative, 5.3% with delayed fetal movement. Out of 113 cases from Group B, majority were post-dated pregnancy i.e. 36.3% followed by 28.3% with oligohydramnios, 13.3% with fetal growth retardation, 6.2 % were Rh negative and 3.5% had gestational hypertension.

70.8% of the pregnant women from Group A were primigravida as compared to 65.5% from Group B. 29.2% of the pregnant women from Group A were multigravida as compared to 34.5% from Group B. This difference in the percentages between two groups was statistically non-significant in the present study ($p>0.05$)

83.2% of the pregnant women from Group A were nullipara as compared to 71.7% from Group B. 10.6% of the pregnant women from Group A were primipara as compared to 18.6% from Group B. 6.2% of the pregnant women from Group A were multipara as compared to 9.7% from Group B. This difference in the percentages between two groups was statistically non-significant in the present study ($p>0.05$)

15.9% of the pregnant women from Group A had past history of abortion as compared to 14.2% from Group B. This difference in the percentages between two groups was statistically non-significant in the present study ($p>0.05$)

15.9% of the pregnant women from Group A had living children as compared to 28.3% from Group B. This difference in the percentages between two groups was statistically significant in the present study ($p < 0.05$)

8% of the pregnant women from Group A were overweight and obese as compared to 13.3% from Group B. This difference in the percentages between two groups was statistically non-significant in the present study ($p > 0.05$)

59.3% of the pregnant women from Group A went into active labour as compared to 55.8% from Group B. This difference in the percentages between two groups was statistically non-significant in the present study ($p > 0.05$)

55.8% of the pregnant women from Group A delivered with normal vaginal delivery as compared to 47.8% from Group B. 44.2% of the pregnant women from Group A underwent LSCS as mode of delivery as compared to 52.2% from Group B. This difference in the percentages between two groups was statistically non-significant in the present study ($p > 0.05$)

51.3% of the pregnant women from Group A delivered with spontaneous normal vaginal delivery as compared to 45.1% from Group B. 4.4% of the pregnant women from Group A delivered with instrumental delivery as compared to 2.7% from Group B. This difference in the percentages between two groups was statistically non-significant in the present study ($p > 0.05$)

44.2% of the pregnant women from Group A underwent LSCS as mode of delivery as compared to 52.2% from Group B. In 19.5% women from Group A had fetal distress as indication of LSCS as compared to 11.5% from Group B. 13.3% women from Group A had failed induction as indication of LSCS as compared to 26.5% from Group B. 7.1% women from Group A had meconium-stained liquor as

indication of LSCS as compared to 8.8% from Group B. This difference in the percentages between two groups with respect to LSCS indications was found statistically significant in the present study ($p < 0.05$).

No maternal adverse outcome was observed in either of the group in the present study.

We observed no single newborn or still birth in either of the group in the present study.

48.7% of the newborns from Group A were female babies as compared to 54.9% from Group B. 51.3% of the newborns from Group A were male babies as compared to 45.1% from Group B.

NICU admission rate in Group A was 28.3% as compared to 20.4% from Group B. This difference in the percentages between two groups with respect to NICU admission rate was statistically non-significant in the present study ($p > 0.05$).

Distribution according to indications for NICU admission revealed that 18.6% of newborns from Group A had hyperbilirubinemia as compared to 15% from Group B. 7.1% newborns from Group A had respiratory distress as compared to 3.5 % from Group B. 1.8% newborns from Group A had hypoglycaemia as compared to 0.9% from Group B. This difference in the percentages between two groups with respect to indications for NICU admission was statistically non-significant in the present study ($p > 0.05$).

Mode of delivery in active stage of labour revealed that 4.5% of women from Group A underwent LSCS as compared to 15.9% from Group B. 95.5% of women from Group A underwent normal vaginal delivery as compared to 84.1% from Group

B. This difference in the percentages between two groups with respect to indications for NICU admission was statistically non-significant in the present study ($p>0.05$).

Mean age of the cases from Group A and Group B was 24.66 ± 3.54 and 24.94 ± 3.81 years respectively. We observed no statistically significant difference between two groups with respect to age of the mothers ($p>0.05$).

Mean gestational age of the women at enrolment from Group A and Group B was 38.82 ± 1.23 and 38.87 ± 1.17 weeks respectively. We observed no statistically significant difference between two groups with respect to gestational age of the mothers ($p>0.05$).

Mean pre induction Bishop's score from Group A and Group B was 2.03 ± 2.09 and 2.85 ± 2.02 weeks respectively. We observed statistically significant difference between two groups with respect to pre induction Bishop's score ($p<0.05$). It means pre induction Bishop's score was significantly higher in Group B compared to Group A.

Mean BMI of the women from Group A and Group B was 22.46 ± 2.21 and 23.15 ± 2.76 respectively. We observed statistically significant difference between two groups with respect to BMI ($p<0.05$). It means BMI was significantly higher in Group B compared to Group A.

Mean birth weight from Group A and Group B was 2.77 ± 0.38 and 2.89 ± 0.41 respectively. We observed statistically significant difference between two groups with respect to birth weight ($p<0.05$). It means birth weight was significantly higher in Group B compared to Group A.

Mean APGAR score at 1 minute from Group A and Group B was 7.02 ± 0.46 and 7.04 ± 0.21 respectively. We observed statistically no significant difference between two group with respect to APGAR score at 1 minute ($p > 0.05$).

Mean APGAR score at 5 minutes from Group A and Group B was 8.09 ± 0.59 and 8.2 ± 0.4 respectively. We observed statistically no significant difference between two group with respect to APGAR score at 5 minutes ($p > 0.05$).

Mean duration of hospitalisation from Group A and Group B was 6.39 ± 1.91 and 6.19 ± 1.5 days respectively. We observed statistically no significant difference between two group with respect to duration of hospitalisation ($p > 0.05$).

Mean induction to delivery interval in Group A and Group B was 995.06 ± 589.65 and 1139.27 ± 1480.99 minutes respectively. We observed statistically no significant difference between two group with respect to induction to delivery interval ($p > 0.05$).

Mean numbers of misoprostol in Group A and Group B was 2.98 ± 2.13 and 3.67 ± 1.87 respectively. We observed statistically significant difference between two group with respect to numbers of misoprostol ($p < 0.05$). It means number of doses of misoprostol required in Group B was more as compared to Group A.

16 women delivered with only mifepristone in Group A i.e. 7.1%.

SUMMARY

In this present study we found clinically significant improvement (though not statistically significant) in Bishop's score in group A (Tab. Mifepristone with Tab. Misoprostol) compared with Group B (Tab. Misoprostol) in induction of labour.

Mode of delivery in active stage of labour revealed that 4.5% of women from Group A underwent LSCS as compared to 15.9% from Group B stating no significant difference between two groups. It means Tab. Mifepristone with Tab. Misoprostol is as good as Tab. Misoprostol alone in our study.

NICU admission rate in Group A was 28.3% as compared to 20.4% from Group B. This difference in the percentages between two groups with respect to NICU admission rate was statistically non-significant in the present study ($p>0.05$).

We observed statistically no significant difference between two groups with respect to induction to delivery interval ($p>0.05$).

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ANEXURE: I- INFORMED CONSENT FORM

KAHERs JNMC, BELAGAVI

**“EFFECTIVENESS OF MIFEPRISTONE AND MISOPROSTOL V/S
MISOPROSTOL ALONE IN INDUCTION OF LABOR - A RANDOMIZED
CONTROLLED TRIAL”**

Name of Student/Principal Investigator: Dr.

Name of Guide/Co Investigators: Dr.

Objective:

Primary Objective - To determine the effect of mifepristone and misoprostol VS misoprostol alone in induction of labor.

Secondary Objective - To determine the fetomaternal outcome.

Introduction: Tablet Mifepristone is also called as RU (Roussel Uclaf) - 486. It is 19 – nor steroid with potent competitive anti-progesterone and significant anti-glucocorticoid activity. Mifepristone is used as a pre-treatment to prime the cervix adequately.³ Mifepristone produced a modification in the consistency of the cervix with a statistical improvement in cervical calibration.⁴ Mifepristone causes blockage of progesterone receptors and inhibits the activity of progesterone at cellular level with potent anti progestogenic, antiglucocorticoid and a weak anti androgenic action and causes cervical ripening effect.⁵ Mifepristone has minimal effects on uterine contractility and increase the sensitivity to prostaglandins and convert the quiet pregnant uterus into organ of spontaneous activity.⁴ Various studies conducted on induction of labor in live term pregnancies with Mifepristone in doses of 200-400mg has shown to improve cervical ripening and rates of induction of labor with no

apparent maternal or fetal side effects.^{6,7,8,9} Also some studies have shown that combined Mifepristone with Misoprostol is safe, efficient and economical and convenient induction agent for initiation of labor,¹⁰ but the caesarean section rate was significantly lower in induction with Mifepristone alone but found more with Mifepristone followed by tablet Misoprostol.¹¹

To increase the success of a vaginal delivery with an unfavourable cervix, several effective cervical ripening methods can be applied that include non-pharmacological and pharmacological options.¹² cervical ripening is one of the most important factors for successful induction of labour (IOL). Mifepristone provides an interesting new alternative to classic uterotonic agents for IOL. Unlike Prostaglandins, mifepristone has minimal effects on uterine contractility as it induces labour mainly by cervical ripening and it is associated with lesser maternal and fetal complications.

There is evidence, from the trials, that mifepristone does induce both ripening of the cervix, and labour.¹⁶

Mifepristone (RU 486) is a potent antiprogesterone and antiglucocorticoid weak anti-androgen. Increases sensitivity of the uterus to prostaglandin was also seen. It leads to decreased induction delivery interval and lesser doses of misoprostol and subsequently lesser side effects. The doses of misoprostol and routes of administration are highly variable.¹⁷

Explanation of procedure: Each number will allocate the patient to either treatment group A or B.

Group A will receive T. Mifepristone 200mg orally on day 1 which is followed by T. Misoprostol 25 mcg intravaginally after 24 hrs and continued 4 hrly till patient goes into active labor with maximum six tablets.

Group B will receive T. Misoprostol 25 mcg intravaginally and continued 25 mcg 4 hrly till patient went in active labor with maximum six tablets.

The women will be followed up till they went labour with bishop score >6 and cervical dilatation >4cm.

Withdrawal from participation in the study: Participation in this study is voluntary. You will be free to decide whether to participate in this study or continue participation once enrolled. In case you decide to withdraw your participation, you are free to do so. However, please convey the decision to the principal investigator.

Possible benefits from participating in the study: You will/will not have nor get any benefits by participating in this study. The data gathered will help the population at large.

Possible risks from participating in the study: There are no risks involved in participating in this study.

Privacy and confidentiality: The information collected from you will be coded, to prevent any person from identifying you. Your identity will never be revealed. The data collected from you will be kept confidential and only processed or aggregated data will be used for publication.

Financial incentives: You will not receive any payment for participating in this study. **Authorization for publication of aggregated data:** Results obtained after processing of the aggregated data will be published for scientific purposes and or presented to scientific groups.

However, your identity will never be revealed.

Questions: In case of any questions with regard to this study, you are free to contact:
If you have any question or complaints with regard to your right as study participant you may contact Dr. Harsha Hegde, Chairperson, Ethical committee of JNMC, 0831-2473777 Extension 4052.

Legal rights: By signing this consent form, we are not waving any of your legal rights.

CONSENT STATEMENT

I am making a voluntary decision to participate in the study
**“EFFECTIVENESS OF MIFEPRISTONE AND MISOPROSTOL VS
MISOPROSTOL ALONE IN INDUCTION OF LABOR - A
RANDOMIZED CONTROLLED TRIAL”**. My signature

Below indicates that I have decided to participate and I have read the
information provided above or the information provided above has been read
to me in the language that I understand best. I was given the opportunity to ask
questions and that they have been answered to my satisfaction.

Name of the participant:

Signature or left thumb impression of the participant:

Name of the witness:

Signature or left thumb impression of the witness:

Name of the investigator:

Signature of the investigator:

ANEXURE: II- PROFORMA
SCREENING FORM

Screening number:

Date of screening:

1. Is Gestational Age ≥ 37 weeks?	YES	NO
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LMP -

EDD -

USG 1st Trimester -

EDD Actual -

Gestational Age -

2. Inclusion Criteria -

a) Women with USG confirmed Singleton pregnancy of 37-41 weeks duration

YES	NO
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b) Cephalic presentation	YES	NO
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c) No contraindications to vaginal delivery	YES	NO
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d) Reactive CTG	YES	NO
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e) Bishop score < 6	YES	NO
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f) Patient meets 1 or 2 of the following criteria

i. Rh negative pregnancy

ii. Fetal macrosomia

iii. Hypertensive disorders of pregnancy

iv. Oligohydramnios

v. Maternal diabetes

vi. Postdated pregnancy	YES	NO
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g) Intact membranes	YES	NO
h) Fetal growth restriction	YES	NO
3. Exclusion Criteria -		
a) Previous Lower segment caesarean Section (LSCS):	YES	NO
b) Prior significant uterine or pelvic surgeries	YES	NO
c) Malpresentations	YES	NO
d) Associated disorder (renal disorders, hepatic disorders, coagulopathies, eard/o, anemia, thyroid, epilepsy, asthma)	YES	NO
e) Premature rupture of membrane(PROM)	YES	NO
f) Gross Mullerian and Congenital Anomalies	YES	NO
g) Hypersensitivity to Prostaglandins & Mifepristone	YES	NO
h) Placenta Previa,/ vasa Previa	YES	NO
i) Active genital herpes	YES	NO
j) Cephalo Pelvic Disproportion	YES	NO
k) Patient not willing to participate	YES	NO
4. Is the patient eligible for study	YES	NO

RANDOMIZATION FORM

Eligibility:		
Is she eligible for the study?	YES	NO
Consent:		
Did the women give consent for the study?	YES	NO
Enrolment:		
Was the woman enrolled in the study?	YES	NO
Was the woman randomized?	YES	NO

If not randomized, indicate reason -

- Withdrawal from study

- Other

Date of Randomization

--	--	--	--	--	--	--	--

(dd/mm/yyyy)

Time of Randomization

--	--	--	--

Participant Number (see sealed envelope)

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Investigator's name:

Signature:

PROFORMA

IP Number:

First Name :

Middle Name :

Last Name :

Husband's Name :

Age(Years) :

Address :

H. No -

Street -

Taluka -

District -

Phone Number -

Landline (Optional) -

Registered -

Date of Admission -

Time of Admission -

Unregistered -

Date of delivery:

History of presenting illness

1. Months of amenorrhoea:

2. Appreciating fetal movement: YES NO

3. Chief complaints

Pain abdomen	YES	NO
PV bleed	YES	NO
PV leak	YES	NO
Others (Specify)		

Obstetric history

Married life -

Obstetric score: Gravida Para Live Abortion

LMP -

EDD -

SCANS

1. Dating scan -

a) Gestational Sac -

b) Yolk Sac -

c) Cardiac activity -

d) FHS -

- e) CRL -
- f) AGA -
- g) CEDD -
- h) Any significant pathology -

2. Anomaly Scan -

- a) Single/Multiple gestation -
- b) Cardiac activity -
- c) Lie -
- d) Placenta -
- e) Liquor -
- f) BPD -
- g) HC -
- h) AC -
- i) FL -
- j) EFW -
- k) AGA -
- l) Cervical Length -
- m) Any gross anomalies -

3. Growth Scan -

- a) Single/multiple gestation -
- b) Cardiac activity -
- c) Lie -
- d) Placenta -
- e) Liquor -
- f) BPD -
- g) HC -
- h) AC -
- i) FL -
- j) EFW -
- k) AGA -
- l) Doppler -

General Examination -

PR -

BP -

RR -

Temp -

Height -

Weight -

BMI -

Pallor - YES NO

Icterus - YES NO

Edema - YES NO

Thyroid/ Breast/ Spine:

Systemic examination

CVS:

Respiratory:

P/A: Uterus Size -

Relaxed -

Contractions (if any, specify):

Presentation -

Engaged -

Non engaged -

FHR -

CEFW -

Diagnosis:

LABOUR DETAILS:

Cervical Dilatation							
Effacement/length							
Station							
Consistency							
Position							
Total score							
Uterine contractions							
FHR							
Intervention done							

Outcome: Success/Failure:

Induction to delivery intervals (Minutes):

Maternal outcome:

Mode of delivery:

Vaginal

LSCS

If Vaginal: Normal:

Ventouse:

Forceps:

If emergency LSCS, then indication:

- a) Fetal concerns
- b) Inadequate progress of labor
- c) Failed induction
- d) Others (specify)

Maternal complications:

Chorioamnionitis: YES NO

Postpartum metritis: YES NO

Uterine Hypertonus - YES NO

Tachysystole - YES NO

Hospital Stay (Days):

NEWBORN OUTCOME:

Live Birth: YES NO

Still Birth: YES NO

Birth Weight:

Apgar - 1 minute

5 minute

Cord blood PH done, if Yes then PH _

Meconium at delivery-

NICU admission: YES NO

Reason for admission in NICU:

Duration of hospital stay:

Date of Discharge: _____

ANEXURE: III
MASTER CHART

